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POSTACIDOTIC STATE OF INFANTILE DIARRHEA: SYMPTOMS AND CHEMICAL DATA

Postacidotic Hypocalcemia and Associated Decreases in Levels of Potassium, Phosphorus and Phosphatase in the Plasma

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THE MAIN attention of investigators of infantile diarrhea in the past has been directed toward understanding of the chemical events leading to acidosis and dehydration. From a recognition of the severity of the chemical changes, concepts and procedures for correcting the acidosis and the losses of extracellular fluid have been developed. However, despite great theoretic and practical advances the fatality from infantile diarrhea has continued to be high. To some extent this high fatality still may be accounted for by acidosis, which may recur during protracted diarrhea. Many infants, however, die without acidosis, dehydration or retention of nitrogen. To explain such deaths of infants, concepts of "toxemia" or of "irreversible" damage to the tissue have been introduced.

It is the purpose of this paper to report the chemical changes and the signs and symptoms of infants with diarrhea during acidosis and following recovery from acidosis. The data to be reported indicate profound changes in the level of calcium, potassium, phosphorus and phosphatase in the plasma during the postacidotic period. In explanation of these changes the concept of two phases of the diarrheal illness has been evolved: (1) the phase of acidosis and dehydration, during which losses of extracellular and intracellular ions and fluids occur, and (2) the postacidotic phase, during which, after correction of deficits of extracellular ions, depletion of the nonextracellular ions ensues because of avid uptake of these ions by soft tissues and bone. Plasma depletion of these ions is attended by pronounced signs and symptoms.

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CHEMICAL CHANGES

In tables 1 to 4 are presented data on the chemical changes of several constituents of the plasma of 58 infants with diarrhea in acidosis and during the postacidotic period. Included are notes concerning the course and the symptoms of the patients. In table 1 are summarized the data on the calcium and carbon dioxide contents of the plasma of 22 patients at the time of their acidosis and at varying periods thereafter. Data on an additional 15 patients, shown in table 2, illustrate concomitant changes in levels of phosphorus, potassium and phosphatase. In table 3 the simultaneously determined values for levels of calcium, phosphorus and protein in the serum of 14 other infants are listed for the purpose of assessing possible interrelationships between the levels of calcium and of protein. In table 4, finally, are presented composite changes of the several constituents of the plasma of 6 patients with recurrent acidosis who were studied most extensively.

Turning to a consideration of the chemical data, one may first examine changes of calcium. It may be seen that generally in patients during acidosis levels of calcium above 9 mg. per hundred cubic centimeters of plasma were measured. Occasionally levels above the upper limit of normal were observed, e. g., in cases 15, 18 and 21, in which values of 11.2, 12.5 and 11.5 mg. per hundred cubic centimeters, respectively, were measured. Four patients (cases 11, 38, 49 and 58) were admitted with calcium levels below 9 mg. per hundred cubic centimeters. Patient J. S. (case 11) had received an unspecified amount of sodium bicarbonate at home; A. S. (case 38) was extremely malnourished, and A. C. (case 49) was a premature infant with a history of diarrhea of several days' duration. S. S. (case 58) had a low carbon dioxide content of the plasma but had a normal p_H, and differed from all other patients in that his diarrhea was caused by administration of castor oil.

In the postacidotic period, with return of the carbon dioxide content to normal a drop in the level of calcium of widely varying magnitude occurred. The extent of the fall ranged from as much as 4.5 mg. (case 2) to as little as 1 mg. per hundred cubic centimeters. In a small number of cases, not presented in the tables, no significant change in the calcium content occurred during recovery from diarrhea. The lowest values reached, below 6 mg. per hundred cubic centimeters in 3 cases listed in table 1, compare with extreme values of hypocalcemia reported in the literature. Of the 22 patients in table 1, 8 showed values below 7 mg. during their postacidotic period. Of the 55 values of calcium presented in tables 1 to 4, values below 7 mg. were measured in 16, values below 8 mg. in another 10 and values below 9 mg. in 25 patients. At the time of the occurrence of the hypocalcemia the carbon dioxide content rarely exceeded the normal limits. Generally it ranged from 16 to 26 milliequivalents per liter. Occasionally even lower levels of carbon

dioxide were observed concomitant with hypocalcemia. The time of occurrence of the hypocalcemia with reference to the state of acidosis varied considerably. In T. J. (case 6), a malnourished infant, hypocalcemia with its attendant clinical signs was observed within one hour after an injection of sodium bicarbonate had been given for correction of extreme acidosis. In other cases low levels of calcium were found after periods ranging from twelve hours to four days after the initial state of acidosis. The duration of the hypocalcemia also appeared greatly variable. A transient period of hypocalcemia is illustrated by case 30, in which a recovery from extreme hypocalcemia was noticeable within twelve hours. On the other end of the scale of variation persistent hypocalcemia of seven and nine days' duration was observed in cases 42 and 52.

It would appear from the clinical notes in the tables that among factors favoring the occurrence of severe degrees of hypocalcemia, prematurity and malnutrition, recurrent or protracted diarrhea and the presence of high temperature and pronounced dehydration were prominent. Another factor was the degree of retention of nonprotein nitrogen at the time of admission. Additional data to those listed in the tables are included in the appended case histories and are available for this comparison. The impression was gained that severe degrees of retention of nitrogen presaged marked hypocalcemia. To what extent retention of waste nitrogen per se was the primary element associated with the degree of hypocalcemia is doubtful, since high temperature and severe degrees of dehydration may have been factors predisposing to postacidotic change. The possible relation of the type of therapy employed to the chemical changes of the postacidotic period is a question of considerable practical importance but difficult to assess. Many of the infants received sodium bicarbonate intravenously in amounts varying from 0.3 to 0.6 Gm. per kilogram of body weight; others received sodium lactate, usually in somewhat smaller amounts, and most were given parenterally fluids containing sodium chloride and/or dextrose. The type of therapy was related to the severity of the clinical condition of the patient and to the extent of the acidosis, factors which in themselves might be expected to have an effect on the subsequent course and the chemical changes of the patients. A cursory inspection of the clinical notes shows that most gravely ill patients received sodium bicarbonate therapy. They were also the ones who suffered the greatest derangements in the ionic structure of their plasma during the postacidotic period. The data on some cases, however, permit one to reject the hypothesis that the changes in the postacidotic period were more closely related to the administration of bicarbonate than to the underlying condition and course of the patients. Patients, as in cases 2, 32, 36, 38, 42, 44 and 56, who did not receive any alkalizing therapy and expe-

TABLE 1.—*Hypocalcemia During the Postacidotic Period in Infants with Diarrhea*

Case	Patient	Age, Mo.	Weight, Gm.	Chemical Data: Carbon Dioxide, mEq. per Liter	Chemical Data: Calcium, Mg. per 100 Cc.	Time of Sample Relative to Admission, Days	Duration of Diarrhea Before Admission, Days	Clinical Notes: Condition of Patient	Clinical Notes: Other Remarks and Outcome of Illness
1	H. H.	1	2,200	6.7	10.1	0	?	Extremely dehydrated and malnourished; temperature 95 F.; 1.6 Gm. sodium bicarbonate administered	
				17.5	5.6	2	..	Convulsing, mottled cyanosis, rapid respirations, abdomen distended, nystagmus, carpopedal spasms; diarrhea diminished; after intravenous administration of 10 cc. of 10% calcium gluconate somewhat improved	
				21.6	10.6	3	..	Condition critical	Died 12 hours later; necropsy: lobular pneumonia; congestion of lungs and abdominal viscera, enteritis
2	N. W.	12	8,600	16.1	9.3	0	14	Dehydrated, eyes dull; lethargic; temperature 106.8 F.	
				14.5	5.8	1	..	Diarrhea and hydration improved; extremely lethargic and irritable; 5 Gm. calcium gluconate daily for 4 days	Recovery uneventful
3	C. P.	1	3,400	6.3	9.8	0	3	Dehydrated; extremely ill; temperature 100 F.; 2.2 Gm. sodium bicarbonate administered	
				25.0	6.0	2	..	No diarrhea for 1 day; edematous; irritable, extremely flushed; carpopedal spasm; Chvostek reaction positive; temperature 103 F.; 3 Gm. calcium chloride daily for 3 days	Recovery uneventful
4	M. W.	1	4,100	5.4	....	0	7	Severely dehydrated, emaciated, cyanotic; temperature 96.2 F.; 3.0 Gm. sodium bicarbonate administered	
				19.4	6.0	½	..	Extremities twitching; respirations labored; cyanotic, abdomen distended; bradycardia (84/min.); 1 bloody stool; no diarrhea; temperature 104 F.; convulsions stopped after injection of 10 cc. of 10% calcium gluconate. 1 Gm. calcium chloride daily given for 2 days	

					32.2	26.0	6	..	Postmortem sample: cardiac arrest occurred immediately after injection of 10 cc. of 10% calcium gluconate for recurrence of convulsions	
	5	C. U.	4	3,800	7.8	....	0	14	Dehydrated and ill; temperature 102 F.; 1.8 Gm. sodium bicarbonate administered	
					25.1	6.2	1	..	Spasmodic respirations; nystagmus, generalized clonic movements, diarrhea stopped; 25 min. after administration of 2 Gm. calcium chloride symptoms subsided; 3 Gm. calcium chloride daily for 5 days	Recovery uneventful
	6	T. J.	3	2,600	7.3	9.0	0	2	Critical, extremely dehydrated; temperature 102 F.; 2.2 Gm. sodium bicarbonate administered	Premature, congenital cataracts, rickets ?
					16.2	6.5	1/24	..	Convulsing, shallow respirations	Died 5 hours later
						8.5	5/24	..	Postmortem sample	
	7	J. P.	2	3,100	19.1	....	0	4	Dehydrated; temperature 99 F.; poorly nourished, diarrhea stopped	
					27.4	6.6	3	..	Abdomen distended; vomited once; cyanotic, shallow breathing with periods of apnea, nystagmus; no diarrhea	Died 5 hours later
	8	K. S.	8	6,200	11.9	9.4	0	14	Severely dehydrated; temperature 104 F.; 3.5 Gm. sodium bicarbonate administered	
					20.3	6.9	2	..	Pale, listless, abdomen distended; carpopedal spasms; temperature returned to 104 F.; no diarrhea for 1 day	Convulsed and died 6 hours later; spinal fluid protein 54 mg. per 100 cc.
	9	P. J.	½	1,400	6.7	....	15	3	Severely dehydrated; 90 cc. m/6 sodium lactate administered	Twin, diarrhea of the newborn
					...	7.2	16	..	Respiratory difficulty; bradycardia, hematuria and hematemesis	Died 1 hour later; necropsy: subcapsular renal and subpleural petechiae; cerebral congestion

TABLE 1.—*Hypocalcemia During the Postacidotic Period in Infants with Diarrhea—Continued*

Case	Patient	Age, Mo.	Weight, Gm.	Chemical Data: Carbon Dioxide, mEq. per Liter	Chemical Data: Calcium, Mg. per 100 Cc.	Time of Sample Relative to Admission, Days	Duration of Diarrhea Before Admission, Days	Clinical Notes: Condition of Patient	Clinical Notes: Other Remarks and Outcome of Illness
10	J. O.	2	3,300	11.7	10.4	0	10	Dehydrated and lethargic; malnourished; temperature 101 F.; 0.75 Gm. sodium bicarbonate administered	
				20.4	7.5	1	..	Somewhat irritable; diarrhea improved.....	Recovered
11	J. S.	3	5,000	17.4	8.5	0	1	Dehydrated and ill looking; well nourished; temperature 106 F.	History of tremors; received sodium bicarbonate orally at home in unknown amount
				25.5	7.5	1	..	Irritable; edematous; breathing labored; diarrhea stopped; 3 Gm. calcium chloride daily for 3 days	Improved rapidly and recovered
12	R. W.	3	3,200	7.8	....	0	21	Severely dehydrated; temperature 100 F.; 1.8 Gm. sodium bicarbonate administered	
				14.8	7.9	1	..	Edematous, breathing with difficulty; cyanotic, abdomen distended; Chvostek reaction positive; clonic convulsions; hematemesis, diarrhea stopped; 2.0 Gm. calcium chloride administered; vomiting and tetanic movements stopped 40 min. later; 2 days later received 1.9 Gm. sodium bicarbonate and stopped breathing 15 min. later	
13	J. H.	7	5,800	14.9	9.6	0	1	Moderately dehydrated and irritable	
				16.6	8.0	1	..	Diarrhea stopped	Recovered
14	P. A.	5	5,000	6.5	9.4	0	2	Markedly dehydrated and ill; 3 Gm. sodium bicarbonate administered	
				25.3	8.2	1	..	Diarrhea greatly improved	
				25.0	10.0	3	..	Doing well	Recovered

15	J. H.	1	1,900	11.8	11.2	0	4	Moribund; underdeveloped and nourished; skin grayish blue; 1.2 Gm. sodium bicarbonate administered	Premature twin
				18.8	8.3	4	..	Diarrhea unabated; vomiting fecal material	Died 1 day later; necropsy: dysentery
16	L. W.	7	5,100	13.2	9.9	0	4	Malnourished, acutely ill; temperature 101.5 F.; 1.5 Gm. sodium bicarbonate administered	Second bout of diarrhea
				22.4	8.3	2	..	Diarrhea improved, on formula.....	Recovered
17	M. L.	3	3,000	11.2	10.2	0	6	Moderately dehydrated; 220 cc. m/6 sodium lactate administered	
				21.8	8.4	1	..	Greatly improved	Recovered
18	C. N.	10	4,100	29.2	12.5	0	10	Emaciated, chronically ill; poor skin turgor	Recurrence of diarrhea
				24.7	8.4	3	..	Diarrhea stopped; well hydrated; irritable....	Recovered
19	W. F.	2	4,100	14.0	10.6	0	2	Acutely ill and dehydrated; temperature 99.5 F.	
				18.5	8.8	2	..	On formula, diarrhea improved; irritable, temperature 101 F.; 2 Gm. calcium chloride daily for 5 days	
				18.7	11.2	5	..	On calcium therapy.....	Recovered
20	S. W.	2	2,400	10.3	10.3	0	2	Moderately dehydrated; temperature 100 F.; 1 Gm. sodium bicarbonate administered	Premature
				25.4	8.8	1	..	Diarrhea stopped; puffy under eyes; irritable....	Recovered
21	F. C.	2	3,600	13.8	11.5	0	6	Moderately dehydrated; 240 cc. m/6 sodium lactate administered	
				14.0	9.0	1	..	On formula, diarrhea improved.....	Recovered
22	D. M.	1	2,300	9.0	10.6	0	2	Malnourished and moderately dehydrated; 220 cc. m/6 sodium lactate administered	
				24.7	9.3	1	..	On formula, diarrhea continuing.....	Eventually recovered

TABLE 2.—*Concomitant Changes of Calcium, Phosphorus, Phosphatase and Potassium in the Plasma during the Postacidotic Period*

Case	Patient	Age, Mo.	Weight, Gm.	Chemical Data: Carbon Dioxide, mEq. per Liter	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per Liter	Potassium, mEq. per Liter	Phosphatase, Bodansky Units	Time of Sample Relative to Admission, Days	Duration of Diarrhea Before Admission, Days	Clinical Notes: Condition of Patient	Other Remarks and Outcome of Illness
23	M. Y.	½	2,800	8.2	10.6	7.7	5.1	10.6	0	15 ?	Severely dehydrated, cyanotic; 1.2 Gm. sodium bicarbonate administered	Diarrhea of the newborn
				23.9	9.6	3.0	2.0	4.6	2	....	On formula, improved, but diarrhea continuing	Eventually recovered
24	J. S.	½	3,200	9.3	10.6	5.7	4.4	....	0	15 ?	Severely dehydrated; 1.5 Gm. sodium bicarbonate administered	Diarrhea of the newborn
				13.4	10.2	3.7	3.4	....	2	....	On formula, but diarrhea continuing....	Eventually recovered
25	M. T.	½	3,400	15.3	—	5.5	4.5	6.3	0	15 ?	Mildly dehydrated; 1.4 Gm. sodium bicarbonate administered	Diarrhea of the newborn
				28.7	—	2.7	3.0	4.7	1	....	On formula, diarrhea stopped.....	Recovered
26	J. H.	1	1,900	12.1	9.6	—	4.8	....	0	4	Moribund; cyanotic and dehydrated; absence of subcutaneous fat; 1.2 Gm. sodium bicarbonate administered	Premature twin
				21.3	8.3	—	2.6	....	2	....	Critical; breathing poorly; carpopedal spasms; limbs stiff	Died 2 days later; necropsy: dysentery
27	J. D.	2	3,200	20.4	9.4	4.1	4.4	....	0	5	Emaciated and mildly dehydrated.....	Bronchopneumonia
				26.1	8.0	2.1	2.8	4.0	1	....	On formula, diarrhea improved.....	Recovered
28	R. H.	½	3,200	13.2	—	6.1	5.1	9.4	0	15 ?	Moderately dehydrated	Diarrhea of the newborn
				18.4	—	5.4	3.0	4.9	2	....	On formula, diarrhea improved.....	Recovered
29	M. C.	1	3,200	12.4	—	—	5.1	—	0	3	Moderately dehydrated, cyanotic; 1.2 Gm. sodium bicarbonate administered	
				20.9	—	—	3.1	—	1	....	Still on intravenous therapy; diarrhea improved	Recovered
30	M. H.	9	6,700	7.1	—	7.7	—	—	0	3	Severely dehydrated and poorly nourished; temperature 103 F.; 5 Gm. sodium bicarbonate administered	
				24.3	5.8	—	2.7	—	½	....	Four hours after injection of sodium bicarbonate hyperkinetic; convulsed 6 hours later; temperature rose to 106 F.	

				29.4	7.7	3.7	4.2	—	1	....	Still irritable, Chvostek reaction positive; 3 Gm. calcium chloride daily for 2 days	
				23.3	9.5	5.5	6.0	6.0	6	....	Symptom free	Recovered
31	B. F.	12	7,300	32.8	6.9	1.5	2.8	....	2	10	Edematous, lethargic; bleeding from site of skin punctures (owing to hypoprothrombinemia)	On admission, weak, dehydrated; temperature 96.6 F.
				37.4	6.5	3.0	2.8	—	4	....	Less edematous; bleeding stopped after administration of vitamin K	Recovered
32	J. K.	3	5,100	18.6	9.7	3.4	—	6.7	0	3	Moderately dehydrated; irritable; temperature 102 F.	
				26.2	8.4	2.3	—	4.7	2	....	Pale and listless; diarrhea stopped day before	Recovered
33	D. R.	6	8,600	20.0	10.0	5.5	—	7.1	0	7	Dehydrated, irritable; temperature 103.2 F.	
				24.5	8.4	2.6	—	4.4	1	....	Mildly edematous; no diarrhea	
				24.0	9.5	4.0	—	8.3	7	....	Doing well	Recovered
34	D. B.	6	4,700	11.4	11.2	5.5	—	8.0	0	2	Moderately dehydrated; temperature 102 F.; 220 cc. m/6 sodium lactate administered	
				22.6	8.8	3.8	—	3.5	2	....	Lethargic and irritable; temperature returned to 102 F.	Recovered
35	G. G.	4	6,500	11.7	10.4	—	—	—	11	7	Dehydrated, cyanotic	Second bout of diarrhea
				27.8	8.8	1.9	3.8	3.1	12	....	Hydration improved; diarrhea diminished but child listless; eyes roll around; received 4 mM phosphate* and 10 mM potassium daily for 3 days	Recovered
36	B. B.	4	4,100	22.8	7.9	2.9	—	2.0	2	5	Chronically ill, malnourished; no diarrhea; vomiting frequently; temperature 102 F.	Second bout of diarrhea; had a cyanotic spell and listlessness 4 days before admission
				—	9.4	5.6	—	5.0	16	....	Doing well	Recovered
37	C. G.	6	5,200	22.7	8.1	2.7	—	3.6	2	5	Irritable, somewhat rigid; occasional vomiting	Diarrhea stopped 2 days before admission
				—	10.2	5.7	—	6.6	15	....	Doing well	Recovered

* Mixtures of potassium and sodium phosphate and of potassium and sodium chloride.

TABLE 3.—*The Relationship of Changes in Calcium and Phosporus of the Plasma to the Level of Serum Protein*

Case	Patient	Age, Mo.	Weight, Gm.	Chemical Data: Carbon Dioxide, mEq. per Liter	Chemical Data: Calcium, Mg. per 100 Cc.	Chemical Data: Phosphorus, Mg. per 100 Cc.	Chemical Data: Serum Protein, Gm. per 100 Cc.	Time of Sample Relative to Admission, Days	Duration of Diarrhea Before Admission, Days	Clinical Notes: Condition of Patient	Clinical Notes: Other Remarks and Outcome of Illness
38	A. S.	7	5,900	21.2	8.6	—	5.7	0	14	Dehydrated and cyanotic; temperature 99.5 F.	
				26.3	5.8	1.2	4.6*	4	..	Lethargic, rapid and shallow respirations with periods of apnea; abdomen distended, nystagmus and strabismus; hematuria	Suddenly stopped breathing and died 1 day later; necropsy: venostasis and thrombosis with focal hemorrhages in brain
39	R. J.	12	6,000	9.5	9.4	3.3	6.5	0	7	Poorly nourished and developed; irritable and dehydrated; temperature 102 F.; 5 Gm. sodium bicarbonate administered	Rickets ?
				28.4	8.0	2.1	6.4	1	..	Hyperactive reflexes, limbs stiff; diarrhea continuing	Recovered
40	R. Mc.	10	7,300	8.8	9.3	—	4.7	0	4	Severely dehydrated and well developed; breathing rapidly; temperature 99.6 F.; 5 Gm. sodium bicarbonate administered	
				22.5	8.5	—	4.8	1	..	Drowsy and irritable; diarrhea subsiding.....	Recovered
41	T. R.	2	3,900	7.4	11.1	5.3	6.5	0	10	Emaciated and dehydrated; temperature 100 F.; 2.5 Gm. sodium bicarbonate administered	Second bout of diarrhea
				29.3	8.1	2.3	6.1	3	..	On formula; doing well	
				27.3	9.7	5.3	6.0	7	..	Doing well	Recovered
42	J. E.	8	8,200	14.0	9.7	—	4.3	0	9	Moribund; complete vascular collapse; femoral pulse absent; eyes dull; hardly breathing; temperature 104.2 F.	
				25.7	7.6	1.9	4.4	5	..	Breathing poorly, Biot type; high-pitched respiratory noises; edematous, cyanotic, convulsing mildly; strabismus and nystagmus; diarrhea stopped; temperature 103.2 F.	Spinal fluid yellow; 570 mg. protein per 100 cc.

			9,700	18.3	8.6	2.0	—	7	..	Condition slightly better; edema increased despite administration of 280 cc. of plasma in 2 days; 3 Gm. calcium chloride daily for 5 days	Spinal fluid faintly yellow; 54 mg. protein per 100 cc.
			8,500	22.8	9.1	—	4.4	11	..	Doing well physically, but signs of cerebral damage present	Mental retardation
43	M. C.	12	6,200	11.6	10.6	6.0	4.6	10	21	Severely dehydrated; poorly nourished; breathing deeply; temperature 103 F.; 2 Gm. sodium bicarbonate administered	Mentally retarded; admitted with history of recurrent severe diarrhea
				18.8	8.6	4.6	4.9	11	..	Convulsing, breathing irregularly.....	Died 1 day later
44	D. A.	1	3,000	11.4	11.8	5.8	6.0	19	5	Moderately dehydrated; breathing poorly; diarrhea more severe	Recurrence of diarrhea in hospital
				24.7	6.7	3.1	5.4	21	..	Hydration and general status and diarrhea improved greatly; received 4 mM phosphate * and 10 mM potassium daily for 3 days	
										Had a spell of cyanosis with nystagmus the following day	Eventually recovered; mental retardation ?
45	R. K.	8	6,000	17.7	9.8	—	4.4	0	5	Severely dehydrated; well developed and nourished; temperature 99.6 F.	
				18.1	8.2	2.7	4.6	6	..	Vascular collapse, cyanotic spell, followed by jerking of all limbs; temperature 102.5 F.; 1 Gm. calcium chloride administered	15 minutes after medication quieted down; recovered uneventfully
46	H. R.	2	1,900	6.3	—	7.1	—	0	7	Marasmic, dehydrated; skin without turgor; body fat absent; mummy-like appearance; 0.7 Gm. sodium bicarbonate administered	Recurrence of diarrhea; had left hospital 1 week earlier with incarcerate hernia, which had reduced itself spontaneously
			3,000	17.9	8.4	3.3	4.9	4	..	Edematous, spastic; nystagmus; Chvostek reaction positive; diarrhea stopped; 3 Gm. calcium chloride daily for 5 days	
			2,600	18.4	11.2	—	5.8	9	..	Doing well	Recovered uneventfully

TABLE 3.—*The Relationship of Changes in Calcium and Phosphorus of the Plasma to the Level of Serum Protein—Continued*

Case	Patient	Age, Mo.	Weight, Gm.	Chemical Data: Carbon Dioxide, mEq. per Liter	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Serum Protein, Gm. per 100 Cc.	Time of Sample Relative to Admission, Days	Duration of Diarrhea Before Admission, Days	Clinical Notes: Condition of Patient	Other Remarks and Outcome of Illness
47	E. B.	6	6,000	11.9	10.8	—	6.6	0	6	Moderately dehydrated, lethargic; temperature 103 F.; 1.8 Gm. sodium bicarbonate administered	
				21.7	6.6	—	5.4	1	..	Convulsing, spasmodic respirations; nystagmus; cyanotic, in circulatory collapse, diarrhea stopped; 3 Gm. calcium chloride daily for 5 days	
				26.3	9.0	—	4.4	4	..	Greatly improved, but still somewhat irritable and lethargic	Recovered
48	A. M.	3	3,100	15.8	—	—	—	0	3	Emaciated, moderately dehydrated; temperature 103 F.	
				30.5	8.2	2.4	6.7	3	..	Hydration improved; lethargic and irritable; diarrhea subsided	
				20.2	9.2	4.0	6.0	7	..	Mildly dehydrated	Slight recurrence of diarrhea; recovered
49	M. C.	2	1,900	10.5	7.7	—	—	0	7	Severely dehydrated and emaciated; temperature 99.5 F.; 1 Gm. sodium bicarbonate administered	Premature
				13.0	7.4	2.6	5.4	0.5	..	Vomiting bloody fluid; spasmodic breathing; diarrhea stopped; 2 Gm. calcium chloride daily for 4 days	
			2,700	19.4	9.1	5.2	5.8	10	..	Doing well	Recovered
50	C. P..	6	7,300	17.7	8.6	—	5.3	1	1	1 day of intravenous therapy; diarrhea persistent	Moderately dehydrated on admission
				25.7	9.4	—	4.5	6	..	Doing well	Recovered
51	R. L.	4	2,700	8.5	10.4	4.0	4.9	0	7	Severely dehydrated; lethargic; poorly developed; temperature 99 F.; 3 Gm. sodium bicarbonate administered	Second bout of diarrhea
				25.3	8.8	2.4	—	2	..	Doing well on formula; diarrhea stopped; temperature 101.6 F.	Recovered

* Mixtures of potassium and sodium phosphate and of potassium and sodium chloride.

TABLE 4.—*Composite Changes in the Plasma During the Postacidotic Period*

Case and Patient	Age, Mo.	Weight, Gm.	Chemical Data: p_H	Carbon Dioxide, mEq. per Liter	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per Liter	Phosphatase, Bodansky Units	Potassium, mEq. per Liter	Serum Protein, Gm. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Time of Sample Relative to Admission, Days	Duration of Diarrhea Before Admission, Days	Clinical Notes: Condition of Patient	Other Remarks and Outcome of Illness
52 R. J.	4	4,100	....	7.7	—	—	—	—	4.9	—	0	5	Extremely dehydrated; emaciated; eyes dull; temperature 106 F.; 3.5 Gm. sodium bicarbonate administered; temperature decreased to 98 F.	Second bout of diarrhea
		5,000	....	26.7	6.0	2.5	4.5	—	4.6	—	5	..	Convulsing; edematous; following a blood transfusion respiratory standstill; resuscitation successful; on formula, no diarrhea; temperature 101 F.; 3 Gm. calcium chloride daily for 2 days	Spinal fluid bloody; protein 470 mg. per 100 cc.; previous spinal fluid normal
		4,200	7.44	20.2	7.9	—	—	—	5.8	—	9	..	Greatly improved; edema subsided; no fever	Spinal fluid yellow; 152 mg. protein per 100 cc.
			7.46	26.3	9.6	2.2	6.8	—	5.6	—	12	..	Doing well; residual spasticity....	Recovered physically; mentally retarded
53 T. F.	1	3,700	7.38	21.6	8.4	1.8	4.7	2.5	5.6	—	8	1	Edematous; inspiratory crow; bradycardia (86/min.); systolic murmur; diarrhea improved; temperature 102 F.	Persistent diarrhea and recurrent acidosis requiring repeated corrections since admission
			7.12	10.1	11.3	2.1	6.1	2.3	4.7	30	11	..	Severely dehydrated; diarrhea recurred; temperature 99 F.; 1.5 Gm. sodium bicarbonate administered	
			7.42	27.4	7.0	2.2	—	2.1	5.4	38	16	..	Edematous; shallow respirations; abdomen distended; diarrhea diminished; 1 bloody stool; temperature 106 F.	Died 1 day later; necropsy: subdural hematoma; congestion, distention and thrombotic occlusion of small cerebral vessels

TABLE 4.—*Composite Changes in the Plasma During the Postacidotic Period—Continued*

Case and Patient	Age, Mo.	Weight, Gm.	Chemical Data								Time of Sample Relative to Admission, Days	Duration of Diarrhea Before Admission, Days	Clinical Notes	
			p_H	Carbon Dioxide, mEq. per Liter	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per Liter	Phosphatase, Bodansky Units	Potassium, mEq. per Liter	Serum Protein, Gm. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.			Condition of Patient	Other Remarks and Outcome of Illness
54 F.	0.5	2,700	....	4.6	—	6.5	9.1	—	—	—	0	15?	Severely dehydrated and cyanotic; in next 10 days had recurrent acidosis requiring repeated correction	Diarrhea of the newborn
		3,100	7.39	24.8	6.8	2.7	5.0	3.0	—	42	11	..	Edematous; abdomen distended; vomiting bloody material; cyanotic; hands and feet in flexion; nystagmus and strabismus; bradycardia 80/min.; systolic murmur; no diarrhea	
		3,300	7.50	30.1	7.5	1.5	4.4	3.6	—	—	14	..	Edema increased; condition slightly better; 6 Gm. calcium gluconate daily for 5 days	
		3,000	....	31.1	10.2	4.2	6.4	6.8	—	—	16	..	Edema subsided; pulse 120/min.; eyes coordinating; no diarrhea	Recovered
55 T. G.	0.5	2,700	....	6.5	—	6.7	—	4.4	—	40	0	15?	Moderately dehydrated; breathing rapidly; temperature 100.4 F.; 2 Gm. sodium bicarbonate administered	Diarrhea of the newborn
		2,900	7.40	19.0	8.4	—	—	2.9	—	—	1	..	Diarrhea improved	
		2,800	7.22	11.9	10.3	—	—	3.5	4.1	—	6	..	Dehydrated again; diarrhea more severe; 1.8 Gm. sodium bicarbonate administered	
		3,200	7.41	28.1	8.0	3.2	—	5.1	4.0	—	9	..	Edematous; strabismus; pulse 88/min.; systolic murmur; diarrhea stopped; 3 Gm. calcium chloride daily for 2 days, followed by 4 Gm. calcium gluconate for 5 days	
		2,800	7.37	19.3	11.1	—	—	5.9	5.2	—	12	..	Edema subsided; heart rate and sounds normal; no diarrhea	Recovered

56 G. A.	2	3,500	....	15.6	10.5	—	—	—	—	—	0	7	Marasmic; dehydrated; started on intravenous alimentation because of intractable diarrhea	
			....	27.0	7.0	2.6	7.4	2.7	5.2	—	13	..	Convulsing, bloody discharge from trachea; blood in stools; spasmodic breathing; appears moribund; hypoprothrombinemia; 3 Gm. calcium chloride, 5 mg. vitamin K, 4 mM phosphate* and 10 mM potassium daily for 3 days	
			....	11.8	10.2	7.7	—	5.2	5.6	—	18	..	Condition improved; moderately dehydrated; diarrhea continuing	
		3,700	....	26.4	8.2	—	—	—	6.3	—	22	..	Rapid shallow respirations; strabismus; nystagmus; icteric; Achromobacter pestifer septicemia	
		4,000	....	—	9.6	—	—	—	5.6	—	39	..	Diarrhea and other infections subsided	Recovered physically; mentally retarded
57 H. R.	8	6,400	....	13.6	11.2	—	—	4.8	—	—	20	0	Moderately dehydrated; temperature 104 F.; 3.7 Gm. sodium bicarbonate administered	Admitted with infection of upper respiratory tract; diarrhea developed in hospital
		7,100	7.58	26.6	7.1	2.6	—	2.7	5.5	51	30	..	Somewhat edematous; face stiff; bradycardia (70-80/min.); diarrhea subsiding; 3.0 Gm. calcium chloride, 8 mM phosphate* and 8 mM potassium daily for 3 days	
			7.45	23.3	10.5	4.3	2.4	6.0	5.6	46	47	..	Much improved, no diarrhea.....	Recovered
58 S. S.	1	3,100	7.49	16.7	5.1	14.2	—	—	—	89	0	4	Severely dehydrated; temperature 105 F.	Received large amounts of castor oil at home
			7.44	21.1	5.2	12.7	6.3	5.2	5.3	80	1	..	Convulsing; no diarrhea; temperature 99 F.; 1.0 Gm. calcium chloride daily for 4 days	Spinal fluid slightly yellow; 79 mg. protein per 100 cc.
			....	23.3	7.0	3.6	9.4	5.2	—	37	5	..	Slight twitchings persist; 3.0 Gm. calcium chloride daily for 3 days	
		3,500	....	22.0	9.4	—	—	—	—	—	8	..	Doing well	Recovered physically; mentally retarded ?

* Mixtures of potassium and sodium phosphate and of potassium and sodium chloride.

rienced severe hypocalcemia and others, as in cases 52 to 55, in whom hypocalcemia developed only several days after the administration of bicarbonate, indicate clearly the independence of the changes of the postacidotic phase of diarrhea of the therapeutic correction of the acidosis. The small drop of the calcium level following sodium bicarbonate therapy, as seen in cases 16, 20 and 23, also indirectly supports this view. On the other hand, cases such as 4, 6 and 30, in which hypocalcemia developed in close succession to the administration of sodium bicarbonate, suggest that this therapy may have initiated or hastened postacidotic changes which otherwise might have occurred with greater delay or less suddenness. No evidence is apparent from the data to indicate that the administration of sodium lactate may have given results different from those produced by bicarbonate; nor is this a likely theoretic possibility, for hypocalcemia appeared in almost all cases with a delay of several hours after alkalizing therapy, an interval of time which would have permitted combustion of most of the lactate to carbon dioxide with a result on the ionic balance identical with that of bicarbonate.

Changes of phosphorus, potassium and phosphatase during the postacidotic period concomitant with those of calcium are summarized in table 2. Additional data are contained in tables 3 and 4. It may be seen that in the acidotic period normal or high values of phosphorus and normal values of potassium and phosphatase were observed. In the postacidotic phase consistently decreased values were found for all three constituents. During such periods the phosphorus reached in some cases values below 2 mg. per hundred cubic centimeters (cases 31, 35, 38, 42 and 54), the potassium decreased to values below 3 milliequivalents per liter (in 9 of the 14 cases studied) and the phosphatase dropped to levels below 3 Bodansky units (cases 36 and 57). The data are hardly sufficient to define the duration of the period of lowered levels of the three constituents. A comparison of cases 30 and 31 indicates the great variation. The significance of the low values for phosphorus and potassium is rendered doubtful to some extent by the fact that many of the patients had received intravenous injections of dextrose-containing fluids shortly before the samples of blood were obtained. This circumstance did not obtain in cases 23, 25, 27, 28, 31, 32 and 37; also the extent of the decrease in either ion in many cases (e. g., cases 30 and 35) appears greater than may be reasonably expected to have been due to the effect of the preceding infusion of dextrose alone.

In view of the often stressed interrelationship between the calcium and the protein level in the plasma it appeared of interest to examine the possibility of an intimate dependence of the level of calcium on that of the protein in cases of infantile diarrhea. Table 3 offers data which were obtained on 14 patients concerning this question. Additional

observations are listed in table 4. An inspection of the table leads to the conclusion that the calcium level both in the acidotic and in the postacidotic period is for the most part independent of the level of protein in the serum. This conclusion is indicated by the observation that in the acidotic period similar calcium levels were found associated with protein levels varying from 4.6 to 6.6 Gm. per hundred cubic centimeters (cases 43 and 47), by the fact that in the postacidotic period extreme alterations of the calcium were associated with small changes of protein in the serum (cases 38, 44 and 47) and by the observation of variations of calcium in the presence of either constancy or even opposite change in the level of protein in the serum (cases 39 to 43, 45 and 49 to 51). Case 46 is of particular interest and will be discussed further in the section dealing with the clinical aspects of the postacidotic state. It may suffice to mention here that the patient in this case showed a rise of calcium and protein levels in the plasma and lost edema after he was placed on calcium chloride therapy alone.

Simultaneous and repeated measurements on 6 patients of most or all of the previously discussed constituents of the plasma, presented in table 4, provide further illustration of the pattern of change in the postacidotic period. Of particular interest are cases 53, 55 and 56. These patients experienced alternate periods of acidosis and transient recovery. It may be seen that during each acidotic period a normal level of calcium was measured, followed by a decrease concomitant with restitution of the p_H and carbon dioxide toward normal. The parallelism betweeen acid-base balance and plasma level was not so strict for the other constituents as it was for the calcium. The data in this table provide further indication of the independence of the level of calcium of that of proteins in the serum in infantile diarrhea.

In table 5 are presented data on 3 patients with diarrhea who received excessive amounts of sodium lactate with their formula and who consequently experienced alkalosis in the postacidotic period. Data on these patients, although in line with those observed for others, are separately presented because of their distinguishing feature of a pronounced alkalosis. It may be seen from the table that the p_H following the administration of large amounts of sodium lactate rose to values of 7.56 to 7.66 and the carbon dioxide to 43 to 46 milliequivalents per liter of plasma. During the period of alkalosis the concentration of calcium in the plasma was reduced to a variable degree. No relationship between the level of calcium and that of carbon dioxide or protein is apparent. In all 3 patients low values for potassium were measured. As the p_H and carbon dioxide returned to normal after the administration of calcium chloride the values of calcium and potassium in the plasma rose. An elevation of potassium to levels higher than normal which subsided within a few days was observed in every case.

TABLE 5.—*Observations on Three Patients Who Received Excessive Amounts of Sodium Lactate in the Postacidotic Period*

Case and Patient	Age, Mo.	Weight, Gm.	Chemical Data								Time of Sample Relative to Admission, Days	Duration of Diarrhea Before Admission, Days	Clinical Notes	
			pH	Carbon Dioxide, mEq. per Liter	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per Liter	Phosphatase, Bodansky Units	Potassium, mEq. per Liter	Serum Protein, Gm. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.			Condition of Patient	Other Remarks and Outcome of Illness
59 M. P.	6	4,000	7.30	18.1	10.5	—	—	—	6.5	32	0	21	Undernourished and dehydrated; temperature 103 F.; 2 Gm. sodium bicarbonate administered and patient put on formula containing ⅓ m/6 sodium lactate	
		4,500	—	35.1	7.7	3.4	2.5	—	5.9	30	3	..	Edematous, lethargic, diarrhea persistent; temperature has risen to 101 F. from normal	
			7.06	43.6	6.3	3.0	2.3	2.8	—	—	4	..	More edematous and lethargic; temperature 103 F.; formula discontinued; 3 Gm. calcium chloride daily for 2 days	
			7.39	23.7	9.1	3.5	3.8	6.1	—	—	7	..	Edema disappeared, patient much improved; temperature 98 F.; diarrhea subsided, medication stopped	
					9.3	4.1	7.2	5.4	5.9	—	10	..	Doing well	Recovered

60 D. A.	2	3,800	—	17.1	—	—	—	—	—	43	0	6	Mildly dehydrated; temperature 100 F.; on 4th day formula containing ½ m/6 sodium lactate started	
		4,300	7.56	46.3	9.0	4.0	—	2.8	—	—	6	..	Somewhat edematous and lethargic; temperature spiking to 104 F.; formula discontinued; 3 Gm. calcium chloride daily for 2 days	
		3,900	7.45	28.1	10.7	4.2	—	6.8	—	—	8	..	Edema subsided, more alert; temperature 99 F.; medication discontinued	
		—	—	—	10.0	—	—	5.6	—	—	12	..	Doing well	Recovered
61 E. P.	..	.....	....	....	...	...	...	...	...	..	..	..	Admitted with moderately severe diarrhea, which recurred in hospital	Premature twin
	2	2,000	—	17.8	—	—	—	—	—	—	11	3	Moderately dehydrated; temperature 99 F.; formula containing ⅙ m/6 sodium lactate started	
		3,300	7.58	43.2	8.4	5.6	4.5	2.6	4.8	40	16	..	Severely edematous; suffered a cyanotic spell with respiratory arrest; bradycardia (30-40/min.) and loud systolic murmur; strabismus; temperature 100 F.; edema increased despite administration of 110 cc. of blood and 125 cc. of plasma; diarrhea stopped; formula discontinued; 3 Gm. calcium chloride daily for 2 days	
		2,600	7.43	30.1	11.7	—	—	6.6	5.1	—	18	..	Edema subsided; more alert; heart murmur much fainter; rate returned to normal	
		2,600	—	—	11.9	—	—	5.0	5.8	—	22	..	Doing well; heart sounds normal	Recovered

To test further the relationship of alkalizing therapy to postacidotic change in the plasma the effect of administering sodium bicarbonate in usual therapeutic dosage was studied in 4 infants without diarrhea. The data summarized in table 6 indicate the failure of medication with 0.5 Gm. of sodium bicarbonate per kilogram of body weight, sufficient to elevate the level of carbon dioxide in the plasma by 9 milliequivalents per liter and to affect significantly the level of calcium, phosphorus, potassium or phosphatase in the plasma. The data support the thesis that the changes in the plasma of infants with diarrhea in the postacidotic period were for the most part related to events in the preceding

TABLE 6.—*The Effect of Administering Sodium Bicarbonate to Infants Without Diarrhea* *

Subject	Age, Mo.	Weight, Gm.	Chemical Data						Time of Sample Relative to Medication, Hr.
			p_H	Carbon Dioxide, mEq. per Liter	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Phosphatase, Bodansky Units	Potassium, mEq. per Liter	
W. B.	5	7,900	7.43	18.6	11.0	7.2	9.6	5.6	0
			7.51	27.4	10.6	7.0	11.0	—	½
			7.41	23.7	10.8	7.9	11.2	5.6	20
L. A.	3	4,200	7.43	20.7	9.8	5.4	9.8	4.6	0
			7.53	28.9	9.4	5.2	9.2	4.2	2
			7.39	21.6	9.2	6.4	9.6	5.2	20
B. M.	3	3,800	—	24.3	10.1	4.7	9.5	—	0
			—	24.5	9.5	5.9	8.5	—	24
J. C.	2	3,200	—	25.8	9.5	7.3	20.0	—	0
			—	26.2	10.2	6.7	19.2	—	24

* Each infant received intravenously 0.5 Gm. of sodium bicarbonate per kilogram of body weight, a dose calculated to elevate the level of carbon dioxide in the plasma by 8.7 milliequivalents per liter.

acidotic phase and that alkalizing agents, although modifying the rate of recovery, exert their effect only in patients predisposed to postacidotic change.

For an understanding of the mechanism of postacidotic changes a consideration of the mineral metabolism during acidosis is indicated, for the postacidotic state, representing a reaction of recovery from acidosis, is conditioned and determined by the severity, the acuteness and the duration of the preceding acidotic phase of diarrhea.

The observations documenting the changes of the mineral metabolism during acidosis are manifold; they include studies of various kinds of acidosis by means both of balance experiments and of experiments with main emphasis on changes in the composition of plasma, erythrocytes and tissue. It was recognized early that considerable losses of water,

electrolytes and nitrogenous substances occur in diarrheal states.[1] The losses of electrolytes concern not only the sodium, chloride and bicarbonate ions, which are predominantly extracellular; but also potassium, which is mainly intracellular; calcium, which exists almost entirely in inorganic form in bone; and phosphorus, which occurs in bone and in soft tissue.[1] The negative balance of minerals in diarrhea then arises in a fourfold manner: (1) from insufficient absorption of dietary intake, (2) from obligatory losses during the state of starvation, (3) from losses with the diarrheal stools of digestive juices, i. e., fluids of predominantly extracellular composition and (4) from losses in both feces and urine caused by a specific effect of acidosis. The acidosis of diarrhea is brought about both by preferential loss of bicarbonate ion with cations in diarrheal stools and by the acidosis-producing effects of starvation, infection and renal impairment.[2]

The losses of extracellular electrolyte on the whole are proportional to the reduction in the volume of extracellular fluid; those of calcium and a portion of the phosphorus are due to mobilization of these ions from bone in response to the stimulus of acidosis, and those of potassium and a portion of the phosphorus are caused partly by destruction of

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2. Howland, J., and Marriott, W. M.: Acidosis Occurring with Diarrhea, Am. J. Dis. Child. **11**:309 (May) 1916. Gamble, J. L.: Acidosis and Alkalosis, New England J. Med. **199**:1318, 1928. Darrow, D. C., and Buckman, T. E.: The Volume of the Blood: II. The Volume of the Blood and the Concentration of Crystalloids and Electrolytes in Dehydration and Edema, Am. J. Dis. Child. **36**:248 (Aug.) 1928. Hartmann, A. F.: Chemical Changes Occurring in the Body as the Result of Certain Diseases: I. The Effects of Diarrhea, Vomiting, Dehydration and Oliguria on the Acid-Base Balance of the Plasma of Infants with Mastoiditis, ibid. **35**:557 (April) 1928. Hamilton, B.; Kajdi, L., and Meeker, D.: Acidosis of Acute Diarrhea in Infancy, ibid. **38**:314 (Aug.) 1929. Hoag, L. A., and Marples, E.: Acid-Base Status in Dehydration Accompanying Diarrhea in Infants, ibid. **42**:291 (Aug.) 1931.

protoplasmic material, as evidenced by increased excretion of nitrogen, and partly by a diminution in the volume of intracellular fluid.[3]

In studies primarily concerned with the composition of body fluids and tissues it has been shown that erythrocytes and muscle during acidosis become depleted of potassium and phosphorus.[4] At least in erythrocytes, esters of phosphoric acid, important in the intermediary metabolism of the cell, are a source of readily mobilizable phosphorus during acidosis.[5] The losses of potassium from the cell are in part associated with the changes in the organic phosphate compounds. The concentration of potassium and phosphorus, rarely that of calcium, in the plasma may be found increased in severe acidosis.[4] This probably occurs when the rate of mobilization from the tissues exceeds the rate of excretion and renal impairment develops.

The changes occurring during recovery from the acidotic state have received little attention. It is reasonable to assume that restitution of losses with eventual restoration of a normal composition of the tissues occurs. Available data indeed indicate a positive balance of the minerals which had been lost during acidosis. The dynamics of the process of recovery, however, is not clearly established. There is some evidence indicating that restoration may proceed with such rapidity and intensity as to change the normal relationships between extracellular and intra-

3. Gamble, J. L.; Ross, G. S., and Tisdall, F. F.: Studies of Tetany: I. The Effect of Calcium Chloride Ingestion on the Acid-Base Metabolism of Infants, Am. J. Dis. Child. **25**:455 (June) 1923. Gamble, J. L., and Ross, G. S.: Studies of Tetany: II. The Effect of Ingestion of Hydrochloric Acid Producing Substances on the Acid-Base Metabolism of an Infant and the Probable Manner of Their Action in the Treatment of Tetany, ibid. **25**:470 (June) 1923. Gamble, J. L.; Blackfan, K. D., and Hamilton, B.: A Study of the Diuretic Action of Acid Producing Salts, J. Clin. Investigation **1**:359, 1925. Følling, A.: On the Mechanism of the Ammonium Chloride Acidosis, Acta med. Scandinav. **71**:221, 1929. Farquharson, R. F.; Salter, W. T.; Tibbetts, D. M., and Aub, J. C.: Studies on Calcium and Phosphorus Metabolism: XII. The Effect of the Ingestion of Acid-Producing Substances, J. Clin. Investigation **10**:221, 1931. Atchley, D. W.; Loeb, R. F.; Richards, D. W.; Benedict, E. M., and Driscoll, M. E.: On Diabetic Acidosis: A Detailed Study of Electrolyte Balances Following Withdrawal and Reestablishment of Insulin Therapy, ibid. **12**:297, 1933. Footnote 1.

4. Guest, G. M.: Organic Phosphates of the Blood and Mineral Metabolism in Diabetic Acidosis, Am. J. Dis. Child. **64**:401 (Sept.) 1942; correction, ibid. **64**: 920 (Nov.) 1942.

5. (*a*) Guest.[4] (*b*) Guest, G. M., and Rapoport, S.: Role of Acid-Soluble Phosphorus Compounds in Red Blood Cells in Experimental Rickets, Renal Insufficiency, Pyloric Obstruction, Gastroenteritis, Ammonium Chloride Acidosis and Diabetic Acidosis, Am. J. Dis. Child. **58**:1072 (Nov.) 1939; Changes in the Organic Acid-Soluble Phosphorus of Blood Cells (Especially the Diphosphoglyceric Acid Fraction) in Different Pathologic Conditions: Clinical and Experimental Studies, ibid. **56**:942 (Oct.) 1938; Acid-Soluble Phosphorus Compounds of Red Blood Cells in Diabetic Acidosis, ibid. **60**:450 (Aug.) 1940.

cellular phases of the body. During recovery from diabetic acidosis the urinary excretion of phosphate may become vanishingly small for periods exceeding seven days.[4] Associated with this phenomenon low values, sometimes below 1 mg. per hundred cubic centimeters, of inorganic phosphorus are found in the plasma. Concomitantly the organic phosphorus of the erythrocytes, and its main fraction, diphosphoglyceric acid, increases slowly from abnormally low values to levels which transiently may exceed the normal. Similar changes have been observed during recovery from the acidosis of diarrhea and of ingestion of ammonium chloride.[5b] The potassium content of the plasma during the period of recovery from the acidosis of diabetes, ingestion of ammonium chloride and, as shown here, diarrhea may be exceedingly low, while the potassium of the erythrocytes increases from low levels to values which transiently exceed the normal range.[4] The calcium in the plasma likewise may be decreased in the period of restitution following the acidoses of diabetes and of ingestion of ammonium chloride.[6] At a varying time during recovery from acidosis, whether or not alkali has been administered, values of p_H and of bicarbonate which exceed normal bounds are commonly found.[4]

As suggested in the preceding paragraph the low values for potassium, phosphorus and calcium in the plasma during the period of recovery may be interpreted as an indication of the direction and the rapidity of the movement of these ions between intracellular and extracellular phases. The level in the plasma, representing the resultant between supply and demand, decreases during the period of avid replenishment of the tissues. With completion of the process of cellular restitution normal equilibrium between intracellular and extracellular phases is reestablished with return to normal of the levels in the plasma. The finding of transient increases above the normal in the intracellular concentration of potassium and phosphorus, and of comparable increases of extracellular p_H and bicarbonate during the period of recovery may represent an excessive reaction of the body to the preceding acidosis with its low values of p_H and bicarbonate in the extracellular and of potassium and phosphorus in the intracellular phases. The changes in the metabolism of calcium during the postacidotic period appear to foll a pattern similar to the described for potassium and phosphorus. Here the normal relationships between bone and plasma are disturbed owing to the rapid deposition of calcium in bone following the preceding period of deprivation. The extracellular phases of the body become transiently depleted of calcium with varying secondary effect on the

6. Smith, B., and West, H. F.: Total Inorganic Calcium and Phosphorus in the Blood of Diabetic Patients Showing a Peculiar Symptom Complex, J. A. M. A. **82**:1990 (June 14) 1924. Rapoport, S., and Guest, G. M.: Unpublished data.

functions of the body. The pattern of change during acidosis and the following period of recovery may also be discerned from the data here presented on the composition of the plasma of infants with diarrhea. The great magnitude of the postacidotic changes and the prominence of the alterations of calcium appear in accord with the characteristic metabolism of the infant, in whom, with great lability of the metabolism of electrolytes in general, dehydration and acidosis occur with greatest rapidity and severity and the calcium metabolism is at its most active stage. Furthermore, interference with the intestinal absorption of calcium may be a specific contributory factor to the hypocalcemia of diarrheal disease. Such interference is thought to produce the hypocalcemia found in sprue, celiac disease and a variety of other intestinal disorders.[7] The combined effects of severe acidosis, great activity of the metabolism of bone and inhibition of intestinal absorption predispose the infant with diarrhea to severe postacidotic hypocalcemia.

Because of scanty and contradictory information discussion of the decreased activity of alkaline phosphatase in the plasma of infants during the postacidotic phase of diarrhea must be largely tentative and speculative. The functional significance of the enzyme in the plasma is obscure. According to one, and perhaps the most likely, view, the activity in the plasma is derived from many organs and represents merely an overflow without functional importance.[8] Among the organs contributing to activity in the plasma bone is the most prominent. Although the relative share of the various organs is uncertain, the contribution of bone is undoubtedly much greater in infancy and childhood than in later life. The high activity of plasma phosphatase in early life is thought to be connected with greater activity of the metabolism of bone in general and that of osteoblasts in particular. On the basis of such reasoning the increased activity of plasma in rickets and the decreased one in scurvy[9] have been related to stimulation and inhibition

7. Mackie, T. T.: Vitamin K Deficiency in Absence of Jaundice, New York State J. Med. **40**:987, 1940. Fanconi, G.: Zöliake, Deutsche med. Wchnschr. **64**:1565 and 1607, 1938. Parsons, L. G.: Celiac Disease: Rachford Memorial Lectures, Am. J. Dis. Child. **43**:1293 (May) 1932. Marble, A., and Bauer, W.: Calcium and Phosphorus Metabolism in a Case of Nontropical Sprue with Associated Tetany, Arch. Int. Med. **48**:515 (Sept.) 1931. Harrison, H. E.; Tompsett, R. R., and Barr, D. P.: Serum Potassium in Two Cases of Sprue, Proc. Soc. Exper. Biol. & Med. **54**:314, 1943.

8. Kay, H. D.: Phosphatase in Growth and Disease of Bone, Physiol. Rev. **12**:384, 1932; Plasma Phosphatase: II. The Enzyme in Disease, Particularly in Bone Disease, J. Biol. Chem. **89**:249, 1930. Bodansky, A.: Phosphatase Studies: VI. Non-Osseous Origins of Serum Phosphatase; Its Increase After Ingestion of Carbohydrates, ibid. **104**:473, 1934.

9. Shwachman, H.: Serum Phosphatase in Infantile Scurvy, J. Pediat. **19**:38, 1941. Shwachman, H., and Gould, B. S.: Serum Phosphatase in Experimental

of osteoblastic activity, respectively. Similarly, the decreased phosphatase in the plasma of hypothyroid children [10] has been referred to subnormal growth of bone. The circumstance that in healing rickets with rapid deposition of bone the activity of phosphatase in plasma decreases suggests that osteoblastic activity alone may not be the factor determining the activity of the plasma enzyme. The relative proportion between the number and/or activity of osteoblasts and the availability of substrate may play an important role. In rickets the high value of plasma enzyme may then be caused not solely by stimulation of osteoblastic activity but also in part by the relative lack of available mineral substrate. The elevation of the enzyme activity in the plasma may be thought to arise from the existence of greater amounts of unused phosphatase in bone which find their way into the plasma. Applying these concepts to the observations in infantile diarrhea, one may consider the decreased plasma phosphatase in the postacidotic phase to be caused by rapid deposition of calcium in bone, with less phosphatase remaining unused and less therefore finding its way into the plasma.

MANIFESTATIONS

Although changes in patients with diarrhea, similar to those reported here, have been described by many clinical observers, failure to differentiate between the signs of the acidotic and the postacidotic phase of the illness has obscured the outlines of the picture of the postacidotic syndrome, which, despite a bewildering variety of sometimes vague manifestations, forms a clearly delineated entity. The onset of the postacidotic phase is often ushered in by a sudden diminution of diarrhea. The infant, previously dehydrated, ashen gray in color, restless and breathing deeply, appears relaxed. He is well hydrated, perhaps even somewhat edematous. The skin is pale, often out of proportion to the actual concentration of hemoglobin in the blood. The abdomen is somewhat distended. The respirations appear peaceful, but are apt to be uneven, abdominal, sighing and with short periods of apnea. The infant, while motionless and quiet when untouched, is found to be irritable when handled. The limbs are somewhat stiff. The eyes are closed; when they are opened they do not focus readily. Mild or severe alternating strabismus, conjugate deviations and nystagmoid movements of the eyes appear intermittently. The face appears pale, swollen and with less than the normal expression. Tapping of the cheek or other parts of the face produces twitchings. Other reflexes may be

Scurvy, J. Nutrition **23**:271, 1942. Gould, B. S., and Shwachman, H.: Bone and Tissue Phosphatase in Experimental Scurvy and Studies on the Source of Serum Phosphatase, Am. J. Physiol. **135**:485, 1942.

10. Talbot, N. B.; Hoeffel, G.; Shwachman, H., and Tuohy, E. L.: Serum Phosphatase as an Aid in the Diagnosis of Cretinism and Juvenile Hypothyroidism, Am. J. Dis. Child. **62**:273 (Aug.) 1941.

hyperactive; often ankle clonus is present. The body temperature, which previously had been or had returned to normal, may be intermittently moderately elevated. Feedings are taken poorly.

With greater severity of the condition the edema is more pronounced and generalized, the face has a masklike stiffness and the abdomen is extremely distended. The respirations are of poor quality, with long periods of apnea. Occasionally respiratory difficulty is so great as to suggest obstruction of the airways, but the lungs are clear to auscultation. Expiration appears to be more interfered with than inspiration. High-pitched respiratory noises may be present; rarely a pronounced laryngeal stridor. The respirations may be so labored and the periods of apnea so prolonged that artificial respiration and the administration of mixtures of carbon dioxide and oxygen appear as life-saving measures. Bradycardia and a loud systolic murmur may make their appearance. The skin may be of a blotchy cyanotic color or extremely pale or more rarely a fiery red. Sudden and transient periods of cyanosis may be seen. Slight spontaneous twitchings of face or limbs may occur, culminating in generalized convulsions, which usually are of clonic-tonic rather than of purely tonic character. Occasionally slight twitchings of the muscles of the face and extremities combined with conjugate deviations of the eyes are the only signs of the convulsive tendency. At times generalized convulsions make an unheralded appearance. Hemorrhagic manifestations may be the most prominent symptoms of the postacidotic state. Bloody tenacious mucus fills the throat. Material of the color of coffee grounds or frankly bloody fluid may be regurgitated or vomited. The stools may contain occult or frank blood. Bloody urine may be passed. The spinal fluid may be blood tinged or xanthochromic with an elevated protein content. Occasionally massive subdural bleeding occurs. The patient in the severe postacidotic state if left untreated may die from cerebral hemorrhage, from respiratory standstill or occasionally apparently in cardiac arrest. When the patient survives the acute attack, he may continue in a stuporous and/or convulsant state for several days. Finally the edema subsides, the respirations become less labored and strenuous, the abdominal distention diminishes and complete recovery takes place. Too often, however, it is then found that permanent cerebral damage has resulted. Strabismus, nystagmus and spasticity persist, and mental retardation may be the final outcome of the severe postacidotic state. While only few of the patients exhibit the whole gamut of the manifestations listed, a combination of several of the signs is present in almost all infants with severe postacidotic syndrome.

Several possible classifications of the diverse symptoms of the postacidotic state present themselves; one arrangement, according to the body functions affected, entails division of the manifestations into four groups: The first group includes effects primarily involving neuro-

muscular functions; here one may distinguish central and peripheral effects of hypocalcemia. Among the former may be listed lethargy, irritability, generalized stiffness and convulsions and among the latter carpopedal spasms, laryngeal stridor and mechanical hyperexcitability. Incoordination of the movements of the eyes may perhaps result from either effect. A second group of manifestations involves changes of the respiration, the heart action, the intestinal motility and the color of the skin. These changes may be caused by an imbalance of the autonomous nervous system. The possibility exists that the manifestations may

TABLE 7.—*Incidence of Manifestations of the Postacidotic State in Fifty-Eight Patients with Diarrhea*

	Number of Patients
I. Changes in neuromuscular function	
A. Central effects	
Convulsions	14
Generalized spasticity	4
Lethargy	10
Irritability	13
B. Peripheral effects	
Carpopedal spasms	5
Laryngeal stridor	2
C. Ocular effects	
Nystagmus	11
Strabismus	5
II. Changes in autonomous functions	
Respiratory system	17
Heart	
Bradycardia	6
Systolic murmur	3
Circulatory collapse	3
Abdominal distension	8
Changes in color of the skin	
Pallor	2
Cyanosis	9
Flush	1
III. Changes in hydration and regulation of temperature	
Edema	13
Fever	9
IV. Hemorrhagic manifestations	
Hematemesis	4
Blood in stools	3
Intracranial bleeding	5
Hematuria	2
Other	2

at least in part result from direct involvement of the organs rather than through nervous mediation. A third group of effects appears to concern the general state of hydration and regulation of temperature. Finally, a fourth group of manifestations of hemorrhagic character, involving with predilection the central nervous system and the intestinal tract, may be recognized.

The incidence of manifestations of the postacidotic state in the 58 patients presented in tables 1 to 4 is shown in table 7. The manifestations are arranged in the manner described in the preceding paragraph. An attempt was made to include only manifestations of considerable degree. In evaluating the data it should be remembered, in order to

avoid an exaggerated impression of the frequency of the manifestations, that considerable overlapping occurred. The most severely ill patients showed several of the manifestations, while others remained entirely free of any untoward sign. It may be seen from the compilation that in 14 of the patients convulsions developed in the postacidotic period. Irritability, lethargy and general spasticity were also frequently noted. Since the latter manifestations obviously are difficult to evaluate, only major degrees of these signs were included in the listing. Compared with the frequency of central effects the low incidence of carpopedal and laryngeal spasms appears noteworthy. This observation is in keeping with older statistics concerning the age distribution of central and peripheral signs of tetany. A question may be raised concerning the significance of ocular signs in young infants; however, all instances of nystagmus and strabismus recorded in the table were of considerable degree and occurred suddenly after previous observation of normal ocular coordination. Frequently, unless a fatal outcome intervened, ocular coordination returned to normal within a short period of time. Among the changes of the autonomous functions, those in the character of the respiration were by far the most frequent. They ranged from unevenness of breathing to respiratory arrest. The sudden development of transient bradycardia and of a systolic murmur in infants in the postacidotic state appears of great interest and will be discussed later. Severe degrees of abdominal distention and noticeable changes in color of the skin were among the less frequent manifestations of this group. Among other changes the occurrence of edema was frequent. The degree of edema varied from moderate puffiness of the face, hands and feet to generalized anasarca. In almost all cases the edema was firm and resistant to pitting to a considerable degree. In the same group of signs are listed several instances of sudden elevation of temperature which occurred concomitantly with other signs of the postacidotic state following periods of normal temperature. In no instance was any other cause of the fever found. Of particular interest is the fourth group of symptoms, those of hemorrhagic character. They occurred in the absence of hypoprothrombinemia in all but 2 cases. Aside from bleeding from the gastrointestinal tract, bleeding in the central nervous system appeared most frequent. The 5 cases of intracranial bleeding include 4 in which a xanthrochromic spinal fluid with elevated protein content was obtained and 1 in which petechial hemorrhages and thrombosis of venules in the brain were observed at necropsy. The symptoms observed in the 3 patients with diarrhea in whom alkalosis developed after administration of large amounts of sodium lactate are excluded from table 7. They appear on the whole similar to those seen in other patients in the postacidotic state. A distinguishing feature possibly was the uniform development of pronounced edema in the

cases of alkalosis. Also noteworthy was the transient elevation of temperature, which subsided promptly after the correction of the alkalosis. The phenomenon of a transient bradycardia and of a systolic heart murmur observed in case 61 adds one more instance of this interesting complication of the postacidotic state to those previously recorded.

In view of the concomitance of convulsions and hemorrhagic manifestations an examination of the association of these two signs is of interest. The relevant data are summarized in table 8. Of the 14 patients with convulsions 2 were found to have normal spinal fluid with a protein content below 30 mg. per hundred cubic centimeters; 4 had xanthochromic spinal fluid with grossly elevated protein; 1 had spinal fluid described as clear with a protein content of 54 mg. per hundred cubic centimeters, and another, whose spinal fluid was not examined, showed at necropsy intracerebral bleeding of disseminate character.

TABLE 8.—*Association of Convulsions with Evidence of Intracranial Bleeding*

	Number of Patients with Convulsions
Total	14
Examined	8
Normal spinal fluid	2
Xanthochromic spinal fluid with elevated protein	4
Clear spinal fluid with elevated protein	1
Spinal fluid not examined; bleeding proved at necropsy	1

The relationship between the clinical symptoms and the chemical changes is obviously of the greatest interest for the understanding of the postacidotic state; it appears also difficult to assess. The almost universal association of low levels of calcium with manifestations of the postacidotic state and the effects of administration of calcium on the condition of the patients appear to indicate the etiologic importance of the hypocalcemia.

A connection between hypocalcemia and a tendency to convulsions and increased peripheral excitability of motor nerves appears plausible on the basis of common clinical experience. The relative paucity of peripheral manifestations and the predominance of central and ocular signs in the infants with diarrhea are in keeping with the experience of early clinical observers, who even went so far as to separate the "eclamptic" tetany of the young infant from the form seen in the older infant.[11] These observers also mentioned the frequent occurrence of

11. (*a*) Escherich, T.: Die Tetanie der Kinder, Vienna, A. Hölder, 1909. (*b*) Finkelstein, H.: Lehrbuch der Säuglingskrankheiten, ed. 4, Amsterdam, Elsevier, 1938. (*c*) Nassau, E.: Zur Klinik der manifesten Tetanie im Säuglingsalter, Ztschr. f. Kinderh. **28**:310, 1921. (*d*) Aschenheim, E.: Uebererregbarkeit im Kindesalter, mit besonderer Berücksichtigung der kindlichen Tetanie (pathologischen Spasmophilie), Ergebn. d. inn. Med. u. Kinderh. **17**:153, 1919.

nystagmus, strabismus and conjugate deviations of the eyes of infants with tetany.

An association between the other symptoms of the postacidotic state, in particular those involving autonomic functions, and changes of the plasma calcium may appear more farfetched and unlikely to the present day clinical observer in pediatrics. Therefore a brief review of older pediatric literature, of the literature dealing with the tetany of adults and of that on experimental tetany, all of which indicate complex and broad relationships between hypocalcemia and vascular, autonomic and trophic changes of the body, may be of interest. Early observers have emphasized the derangement of autonomic functions in tetanic states.[12] They recognized disturbances of respiration, ranging from respiratory arrest in inspiration, "respiratory apnea" and "tetanus apnoicus" [11a,b] to milder respiratory difficulties and tachypnea, believed to be caused by spasm of the bronchial muscles.[13] An underlying disturbance of the normal reflex equilibrium of respiration, present even in latent tetany, was demonstrated.[14] Changes of cardiac action were also associated with tetany. Cardiac arrest (cardiac tetany of Ibrahim) was thought to be one of the causes of sudden death of infants with tetany.[15] Frequently bradycardia,[16] rarely tachycardia, and cardiac murmurs were observed.[12] Later studies showed changes in the electrocardiogram consisting of a relative prolongation of the Q-T interval.[17] Changes in the tonus and

12. Falta, W., and Kahn, F.: Klinische Studien über Tetanie mit besonderer Berücksichtigung des vegetativen Nervensystems, Ztschr. f. klin. Med. **74**:108, 1911.

13. Lederer, R.: Ueber "Bronchotetanie," ein noch nicht beschriebenes Krankheitsbild der Spasmophilie, Ztschr. f. Kinderh. **7**:1, 1913. Kassowitz, M.: Ueber chronisches Asthma der Rachitiker, Wien. klin. Wchnschr. **26**:380, 1913.

14. Masslow, M.: Ueber Veränderungen der Atmungskurven bei Kindern mit spasmophilen Symptomen unter dem Einfluss von äusseren Reizen und die Bedeutung dieser Veränderungen für die Diagnose der latenten Tetanie, Monatschr. f. Kinderh. **13**:99, 1914.

15. Ibrahim, J.: Ueber Tetanie der Sphinkteren, der glatten Muskeln und des Herzens bei Säuglingen, Jahrb. f. Kinderh. **72**:346, 1910. Frei, M.: Zur Behandlung des Herzstillstandes bei Spasmophilia, Monatschr. f. Kinderh. **15**:376, 1919. Schiff, E.: Das Spasmophilieherz, Acta pædiat. **3**:57, 1923. Wolff, S.: Zur Kenntnis der Tetany; Herztetanie, Jahrb. f. Kinderh. **58**:59, 1925. Corsdress, O.: Ein Beitrag zur Frage der Herzbeteiligung bei Spasmophilie, Monatschr. f. Kinderh. **33**:137, 1926.

16. Koplik, H.: Heart Action in Spasmophilia, Arch. Pediat. **39**:504, 1922.

17. Carter, E. P., and Andrus, E. C.: QT Interval in Human Electrocardiogram in Absence of Cardiac Disease, J. A. M. A. **78**:1922 (June 17) 1922. Aschenbrenner, R., and Bamberger, P.: Electrocardiographische Untersuchungen an spasmophilen Kindern, Klin. Wchnschr. **14**:1494, 1935. Hecht, H., and Korth, C.: Ueber Wesen und Bedeutung des QT-Intervalles im Elektrokardiogramm, Ztschr. f. Kreislaufforsch. **29**:577, 1937. White, P. D., and Mudd, S. G.: Observations

the motility of the gastrointestinal tract with spasms of the various sphincters have also been recognized.[18] Derangements of vasomotor control, consisting of pallor, erythema, urticaria and hyperhidrosis, were observed and attributed to spasms of the capillaries of the skin.[19] The occurrence of fever and edema, usually of the hands and feet alone but occasionally of more generalized character, has also been described.[20]

The symptoms of tetany in adult patients, although differing in relative distribution from those in infants, include all the forementioned signs. The occurrence of psychotic changes, unknown and, if occurring, difficult to define in infants, appears of particular interest as an indication of subtle effects of hypocalcemia on the central nervous system. Owing to the greater chronicity of the condition in adults trophic changes are often prominent.[21]

Animal experiments, particularly those on parathyroidectomized dogs, also indicate the significance of changes of autonomic regulation in the signs and symptoms of tetany. Tachypnea, fever, vomiting and diarrhea are among the most frequent and prominent manifestations and appear of determining importance in the development of convulsions.[22]

Finally the relationship of hemorrhagic manifestations to hypocalcemia may be considered. Formerly changes in the amount of calcium in the plasma were often sought in various hemorrrhagic diatheses, usually on the basis of the importance of the calcium ion for the clotting of the blood. In no case of disturbance of the clotting mechanism has the role of the calcium been established, nor is it likely that the level of calcium in the plasma may ever be sufficiently decreased as to lead to a marked disturbance of the clotting time. On the other hand, in hypocalcemic states hemorrhagic manifestations have been observed. The occurrence of bloody vomitus and diarrhea has often been noted in parathyroidectomized animals.[22b] Newer studies on dogs [23] and rats [24]

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on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, J. Clin. Investigation **7**:387, 1929. Spealman, C. R.: The Action of Ions on the Mammalian Heart, Am. J. Physiol. **136**:332, 1942.

18. Finkelstein.[11b] Masslow.[14] Footnote 15.

19. Finkelstein.[11b] Falta and Kahn.[12]

20. Lust, F.: Ueber den Einfluss der Alkalien auf die Auslösung spasmophiler Zustände, München. med. Wchnschr. **60**:1482, 1913. Bossert, O.: Ueber die Auslösbarkeit von Ödemen und Carpopedalspasmen bei Spasmophilen durch salzarme Ernährung, Jahrb. f. Kinder. **42**:121, 1920. Footnote 11*a* and *b*.

21. Shelling, D. H.: The Parathyroids in Health and in Disease, St. Louis, C. V. Mosby Company, 1935.

22. (*a*) Shelling.[21] (*b*) Thomson, D. L., and Collip, J. B.: The Parathyroid Glands, Physiol. Rev. **12**:309, 1932.

23. Martin, G. J.: A Calcium Deficiency Syndrome Produced in Growing Animals, Growth **1**:175, 1937.

(Footnotes continued on next page)

on diets extremely low in calcium not only have confirmed the occurrence of a hemorrhagic diathesis in hypocalcemia, but also have indicated the mechanism of the disorder. Animals on the calcium-low diets were found to suffer from widespread hemorrhages, which occurred with predilection in the central nervous system and the gastrointestinal tract. A primary dysfunction of the vascular wall was indicated by histologic studies which showed dilatation of the capillaries and extravasation of erythrocytes. In patients with chronic tetany, usually caused by hypoparathyroidism, disseminated cerebral calcifications have been described, perhaps developing secondary to hemorrhage.[25] The occasional occurrence of elevated protein content and xanthochroma of the spinal fluid in infants with tetany of rickets (unpublished) likewise may indicate the possibility of hypocalcemia as a cause of hemorrhage.

Even though some degree of hypocalcemia was present in all infants with manifestations of the postacidotic state, it is clearly evident from an inspection of the data that no close quantitative relationship between the extent of hypocalcemia and clinical signs and symptoms existed. Occasionally patients with extremely low levels of calcium, as in cases 2 and 44, showed only minor clinical signs, while patients with only moderate hypocalcemia, as in cases 53 and 55, presented the whole range of symptoms of the postacidotic state. Such a discrepancy between extent of chemical and clinical disturbance, while poorly understood, is well known to observers of other types of hypocalcemic tetany. In patients with tetany of rickets or with hypoparathyroidism manifestations of tetany have been noted with calcium levels as high as 9 mg. per hundred cubic centimeters, while the same or other patients have remained remarkably free of symptoms with calcium levels as low as 7 mg. per hundred cubic centimeters.[21] Therefore attempts to divide clinically tetany into manifest and latent forms on the basis of calcium content of the plasma alone have proved unsatisfactory. The association between calcium level and manifestations of tetany is improved but little by estimation of the effect of protein on the level of ionized calcium, for, although the general assumption appears well substantiated that only the ionized calcium is biologically active, factors modifying the action of the calcium ion, yet poorly understood, are recognized to be of great importance. The occurrence of tetany with normal levels

24. Boelter, M. D. D., and Greenberg, D. M.: Severe Calcium Deficiency in Growing Rats: I. Symptoms and Pathology; II. Changes in Chemical Composition, J. Nutrition **21**:61 and 75, 1941. Zucker, T. F., and Berg, B. N.: Calcium Deficiency and Gastric Lesions in the Rat, Proc. Soc. Exper. Biol. & Med. **53**:34, 1943; The Time Factor in the Production of Gastric Lesions on Low Calcium Diets, ibid. **57**:1, 1944.

25. Eaton, L. M., and Haines, S. F.: Parathyroid Insufficiency with Symmetrical Cerebral Calcification: Report of Three Cases, in One of Which Patient Was Treated with Dihydrotachysterol, J. A. M. A. **113**:749 (Aug. 26) 1939.

of calcium during hyperventilation of short duration [23] and the existence of extreme hypocalcemia without signs of tetany in patients with acidosis of nephritis [26] indicate the importance of the p_H per se on the action of the calcium ion apart from its effect on the ionization of protein. The development of tetanic symptoms with normal p_H values during voluntary hyperventilation of subjects with an underlying fixed acidosis [27] appears to indicate an independent effect of the carbon dioxide tension on the development of tetany. Other modifying conditions have been recorded.[28] The variability of the relation between calcium level and tetanic signs has led several observers to deny the primary importance of the calcium in the causation of tetany and to assume the presence of either unknown toxic factors or of unknown unionized forms of calcium in the plasma.[29]

A fair appraisal of the role of calcium in clinical forms of tetany would recognize the importance of low concentrations of calcium as a primary causal factor, which probably is operative only at normal or higher than normal levels of p_H. The development of clinical signs of tetany once hypocalcemia has been established appears determined by a host of additional factors, among which those affecting the general state of reflex excitability of the central and the peripheral nervous system appear of greatest importance.

The occurrence of tetany in infants with diarrhea, stressed in this paper, is by no means a new observation. Frequent occurrence of tetany in the summer months and the importance of antecedent diarrhea in the development of tetany were first observed by Baginsky.[30] Other early observers [31] also referred to the connection of diarrhea and tetany. After the development of micromethods for analysis of the blood the occurrence of hypocalcemia and of attending manifest tetany

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26. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931. Schmidt, C. L. A., and Greenberg, D. M.: Occurrence, Transport and Regulation of Calcium, Magnesium and Phosphorus in the Animal Organism, Physiol. Rev. **15**:297, 1935.

27. Shock, N. W., and Hastings, A. B.: Studies of the Acid-Base Balance of the Blood: IV. Characterization and Interpretation of Displacement of the Acid-Base Balance, J. Biol. Chem. **112**:239, 1935.

28. Shohl, A. T.: Mineral Metabolism, New York, Reinhold Publishing Corporation, 1939. Footnote 26.

29. Greenwald, I.: The Effect of the Administration of Calcium Salts and of Sodium Phosphate upon the Calcium and Phosphorus Metabolism of Thyroparathyroidectomized Dogs, with a Consideration of the Nature of the Calcium Compound of Blood and Their Relation to the Pathogenesis of Tetany, J. Biol. Chem. **67**:1, 1926. Klinke, K.: Der Mineralstoffwechsel: Physiologie und Pathologie, Leipzig, F. Deuticke, 1931.

30. Baginsky, A.: Ueber Tetanie bei Säuglingen, Arch. f. Kinderh. **7**:321, 1886.

31. Escherich.[11a] Finkelstein.[11b] Nassau.[11c]

in infants with diarrhea was reported by Howland and his co-workers [32]; these observers stressed the relation of the hypocalcemia to the administration of sodium bicarbonate, but also noted the occurrence of hypocalcemia in infants who had not received sodium bicarbonate.[33] Low levels of calcium in diarrheal states were also reported by others.[34] The occurrence of tetany and of hemorrhagic symptoms in infants with severe diarrhea was emphasized by Dodd and Minot,[35] who attributed the symptoms to guanidine intoxication. These authors ascribed a beneficial effect to medication with calcium in the management of diarrhea.

Many of the symptoms of hypocalcemia described in the literature were noted in the infants with diarrhea; yet the possible significance of derangements of other ions, in particular potassium and phosphorus, although not clearly evident in this series of patients, cannot be gainsaid. In patients with familiar muscular paralysis [36] and in subjects treated with desoxycorticosterone,[37] lowering of the level of potassium in the serum is associated with muscular paralysis and changes of the electrocardiogram, which shows a decreased height of the T wave. In

32. Howland, J., and Marriott, W. M.: Observations upon Calcium Content of the Blood in Infantile Tetany and upon the Effect of Treatment by Calcium, Quart. J. Med. **11**:289, 1918.

33. Kramer, B.; Tisdall, F. F., and Howland, J.: The Clinical Significance of Calcium Concentration in the Serum of Children, and Possible Errors in Its Determination, Am. J. Dis. Child. **22**:560 (Dec.) 1921.

34. Blum, L., and Looft, A.: L'hypocalcémie dans certains états diarrhéiques: Interprétation de l'action thérapeutique des injections intraveineuses de $CaCl_2$, Compt. rend. Soc. de biol. **91**:194, 1924. Cohen, H.; Miller, P. R., and Kramer, B.: Alimentary Intoxication in Infants: Acid-Base Equilibrium with the Use of Continuous Intravenous Therapy; Preliminary Report, J. Pediat. **3**:299, 1933. Lyon, R. A.; Vandermark, J. G., and Mitchell, A. G.: A Clinical Study of Gastro-Enteritis with Special Reference to the Continuous Intravenous Method of Treatment, Ohio State M. J. **30**:227, 1934.

35. Dodd, K.; Minot, A. S., and Casparis, H.: Guanidine as a Factor in Alimentary Intoxication in Infants, Am. J. Dis. Child. **43**:1 (Jan.) 1932. Minot, A. S., and Dodd, K.: Guanidine Intoxication: Complicating Factor in Certain Clinical Conditions in Children, ibid. **46**:522 (Sept.) 1933.

36. Ferrebee, J. W.; Atchley, D. W., and Loeb, R. F.: A Study of the Electrolyte Physiology in a Case of Familial Periodic Paralysis, J. Clin. Investigation **17**:504, 1938. Pudenz, R. H.; McIntosh, J. F., and McEachern, D.: The Role of Potassium in the Mechanism of Family Periodic Paralysis, ibid. **17**:530, 1938. Stewart, H. J.; Smith, J. J., and Milhorat, A. T.: Electrocardiographic and Serum Potassium Changes in Familial Periodic Paralysis, Am. J. M. Sc. **199**: 789, 1940.

37. Currens, J. H., and White, P. D.: Congestive Heart Failure and Electrocardiographic Abnormalities Resulting from Excessive Desoxycorticosterone Acetate Therapy in Treatment of Addison Disease, Am. Heart J. **28**:611, 1944. Raab, W.: Cardiovascular Effects of Desoxycorticosterone Acetate in Man, ibid. **24**: 365, 1942. Kuhlmann, D., and others: Toxin Effects of Desoxycorticosterone Esters in Dogs, Science **90**:496, 1939.

animals maintained on a diet low in potassium myocardial damage and renal hypertrophy have been noted.[38] In the infants with diarrhea lowered T waves were repeatedly found (unpublished). The occurrence of bradycardia and of systolic murmurs in several of the infants may well be related as much to the changes of the potassium as to those of the calcium.

The possible role of the lowered level of phosphorus in the plasma is obscure. Although hyperphosphatemia produces pronounced effects consisting of vomiting and muscular fibrillation and probably plays a significant part in the complex of symptoms of hypoparathyroidism and uremia,[21] low levels of phosphorus in the plasma have no recognizable clinical effects aside from those relating to the metabolism of bone, unless somatic changes of children with rickets are related to their lack of phosphorus.[39] The lowered level of phosphorus in the plasma of the infants, however, may well have modified significantly the effects of hypocalcemia.

The most severe manifestations of the postacidotic state, such as hemorrhagic diathesis, irregularity of breathing, cardiac dysfunction and abdominal distention, may be thought to be caused by preceding irreversible damage and to represent solely terminal events, signifying the dissolution of the organism. Such a view would be supported with respect to hemorrhagic manifestations by the frequent finding of hemorrhages in agonal states. Histopathologically vascular damage is often evident, thought to be caused by the attending anoxia. Recently, evidence of terminal changes of the clotting mechanism with a decrease of prothrombin time has also been obtained.[40] Experience with the infants with diarrhea in whom on occasion the most severe manifestations were reversible and recent experimental work on the physiologic changes in agonal states [41] may lead to a revision of old concepts of the irreversibility and significance of events usually assumed to presage death.

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CALCIUM THERAPY

In view of the foregoing observations it appeared logical to attempt treatment and if possible prevention of postacidotic symptoms by administration of calcium salts. It was soon found that therapy by the customary single intravenous injection of calcium gluconate in amounts of 0.5 to 1 Gm., while temporarily successful in stopping convulsions, was inadequate in the face of a persistent tendency to hypocalcemia. Therefore more vigorous therapy was tried. In most cases calcium chloride in a dosage of 3.0 Gm. daily was given for a period of two to five days, sometimes followed by further therapy with smaller amounts. Occasionally, with older infants, a larger initial dose was administered for the first twenty-four hours. To premature infants and those under 1 month of age as a rule only 2 Gm. of calcium chloride was given daily. With debilitated infants the dose of calcium was often reduced after the first twenty-four hours; sometimes calcium lactate or gluconate was then substituted for the more efficacious chloride. Because of the dangers inherent in parenteral administration, wherever possible the calcium salts were given orally, the daily amount divided into three or four doses. The 10 per cent solution of calcium chloride was always diluted at least four times with formula, or if food was withheld, with isotonic solution of sodium chloride. At times the medication had to be administered by gavage. In emergencies the intravenous route was employed. In such instances the calcium chloride was diluted to 1 per cent and the gluconate to 2 per cent concentration with isotonic solution of sodium chloride.

Correct timing of the therapy obviously is of the greatest importance, in view of the suddenness of the change from the acidotic to the postacidotic phase in the condition of the patient. The problem is to determine the optimal moment to initiate therapy; it should coincide with a turn in the patient's metabolism from an acidotic trend to one of recovery. Often such felicitous timing has been achieved by close observation of the condition of the patient, frequency of stools and chemical change. Such therapy may be classified as preventive, since early initiation of treatment seemed successful in averting the appearance of a full blown postacidotic state in many patients. The decision as to the correct moment to start medication becomes more difficult when symptoms of the postacidotic state and hypocalcemia occur while diarrhea continues and the patient still is in or again enters a state of acidosis. Such an overlapping of trends is observed in patients with chronic or recurrent diarrhea, when tissues apparently no longer willingly surrender their mineral constituents for excretion and even assert their avidity for nonextracellular ions, while acidosis persists. Under such circumstances hypocalcemia and acidosis may coexist and treatment with calcium chloride carries dangers with it. To such patients calcium lactate or gluconate was given.

Among other means of combating hypocalcemic tendency parathyroid hormone and dihydrotachysterol were used. Experience with these drugs is as yet too limited to permit any definite conclusions.

Although the dosages and schedules are only empiric and approximate, and were suitably changed in practice according to the judgment of the clinical observers, an indication of dosage and duration of medication required may be gained from the study of some of the cases. For instance, in case 58 a dosage of 1 Gm. of calcium chloride daily for four days failed to stop convulsions or to restore the level of calcium in the plasma to normal. Similarly in case 42 the administration of 3 Gm. of calcium chloride for one day failed to suppress the subsequent development of edema and convulsions.

The clinical notes of tables 1 to 5 indicate the effectiveness of calcium therapy. In some patients, as in cases 4, 12 and 45, immediate cessation of convulsions resulted; in others the convulsive tendency diminished more slowly. Several patients appeared to have suffered cerebral damage, so that, while they recovered from their acute illness, permanent sequelae resulted. Some patients died despite institution of calcium therapy. Although some reasonable doubt exists concerning the adequacy of dosage and duration of treatment in several of these cases (cases 4 and 12), such experiences indicate the inadequacy of understanding of the condition of the patients and suggest that hypocalcemia may not be the sole cause of death in the postacidotic state. In addition to the effectiveness of calcium in combating the convulsive tendency, other actions may be mentioned. Among them reversal of neuromuscular dysfunction, including ocular incoordination, was often impressive. A definite effect of calcium on the hemorrhagic tendency of the postacidotic state is clearly indicated from the notes on patients 49 and 54, whose bleeding tendency rapidly receded as the result of calcium therapy alone. If an association between hypocalcemia and hemorrhagic tendency, discussed earlier, is accepted, a therapeutic effect of calcium on the hemorrhagic tendency becomes plausible. The actions of calcium therapy in producing return of normal heart action and subsidence of fever also suggest hypocalcemia as a factor in the causation of these symptoms, although an indirect effect, perhaps by way of influencing the level of potassium, appears possible.

The action of calcium in reducing edema of infants in the postacidotic state appears as one of its most remarkable effects. As seen in cases 42, 46, 52, 54, 55 and in the cases in which there was alkalosis (59 to 61), edema, which in some cases amounted to more than 20 per cent of the body weight and which had proved refractory to administration of plasma and blood, disappeared in the space of two to three days after calcium therapy. The explanation of this impressive effect of calcium appears as obscure as is the development of edema in hypocalcemia. Speculation

may be entertained that since the edema of the patients may be related to their inability to excrete sodium ions, perhaps owing to damage to the renal tubules, in some manner, either by virture of a specific effect of the calcium or solely by its acidifying action, the reabsorption of sodium ions may be decreased. Another explanation of the efficacy of calcium chloride would lie in an increased glomerular filtration fraction. Such an effect might result from changes in the hemodynamic mechanisms affecting blood pressure or tone of capillaries. Whatever the detailed mechanism, and it may not be primarily renal, one may visualize the edema of the postacidotic infant as representing a reaction to preceding dehydration, as an overshooting resulting in an increase above normal of the extracellular volume where previously a deficiency had existed. The addition of calcium chloride, whether owing to a specific calcium effect or by virtue of its acidifying action, may tend to keep the exuberance of the postacidotic reaction within reasonable bounds.

Prevention of postacidotic change is a task of great difficulty; even more difficult is the estimation of the results of preventive measures. As mentioned in a foregoing paragraph, timely administration of calcium often appeared to prevent serious postacidotic manifestations. Another factor affecting the incidence of hypocalcemia seemed to be the type and amount of fluid, in particular electrolyte, administered. It appeared that excessive intake of electrolyte with consequent tendency to edema may be a precipitating or aggravating factor in the development of hypocalcemia. Following institution of a regimen of close control of intake of electrolyte, the incidence of severe hypocalcemia has fallen off considerably in the last year. Combination of the two factors, control of intake of electrolyte and timely administration of calcium, has greatly reduced the dangers of the postacidotic state.

Complications of Calcium Therapy.—The administration of calcium salts, by whatever route, is beset by several considerable dangers which it might be worth while to discuss in some detail. Intravenous injection of calcium salts, if sufficiently rapid, may cause cardiac arrest.[42] Even with injections at customary rates bradycardia often occurs.[43] Since vagal stimulation is the probable cause of the slowing,[42] a fatal outcome of such a happening might be averted by immediate countermeasures. Case 4 illustrates an instance of immediate death following an intravenous injection of calcium gluconate. The patient was a debilitated

42. Hoff, H. E.; Smith, P. K., and Winkler, A. W.: Electrocardiographic Changes and Concentration of Calcium in Serum Following Intravenous Injection of Calcium Chloride, Am. J. Physiol. **125**:162, 1939.

43. Berliner, K.: The Effect of Calcium on the Heart, Am. Heart J. **8**:548, 1933. Clarke, N. E.: The Action of Calcium on the Human Electrocardiogram, ibid. **22**:367, 1941. Berliner, K.: Effect of Calcium Injections on the Human Heart, Am. J. M. Sc. **191**:117, 1936.

infant with poor circulation, a circumstance undoubtedly contributing to poor distribution of calcium and favoring a high concentration of calcium in the blood. The concentration of calcium in the cardiac blood of the patient post mortem was found to be 26 mg. per hundred cubic centimeters. Several other instances of cardiac arrest, fortunately transient, had occurred in the past. To avoid this complication it has become mandatory practice at the Cincinnati Children's Hospital to dilute calcium gluconate to 2 per cent and calcium chloride to 1 per cent concentration for intravenous injection. In addition to the immediate danger to the heart, local effects of slow intravenous infusion of calcium salts have been noted. In gravely debilitated patients with poor circulation, necrotizing lesions affecting the site of injection and surrounding areas have been observed. The presence of low levels of chloride in the plasma appeared to be a factor favoring the development of such lesions. It also seemed that the local effect was enhanced when calcium salts were administered diluted with electrolyte-free solutions of dextrose. In particular dilution with 10 per cent solution of dextrose appeared harmful. On the involved extremity dark red to black areas appeared, which were small and superficial at first and distributed along the course of the vein containing the needle. Soon, however, other, more distant, areas, even on the opposite surface of the limb, were affected. The necroses spread with remarkable speed, and if the injection was not discontinued would involve within the space of a few hours a whole segment of an extremity. In almost all cases the occurrence of the process was discovered in time and the infusions were discontinued. The superficial areas of necrosis then healed with little or no scarring. In 1 case, however, the extent of the necrosis was such as to necessitate an amputation of the lower part of a leg.

The reasons for this effect appear uncertain. Piercing of the vascular wall by the needle was never noted, nor would its occurrence explain the wide spread of the necroses. It might be that in the presence of hypochloremia calcium produces a paralysis of the vessels and that subsequent extravasation of calcium salts leads to deleterious effects on the local tissues. This effect may be enhanced by concomitant effects of hypertonic electrolyte-free solutions administered with the calcium.

Intramuscular administration of calcium salts has not been practiced in view of many reports and earlier experiences of subcutaneous and muscular necroses and formation of abscesses from such injections.

Oral administration of calcium salts likewise is not free of danger. Concentrated solutions of calcium chloride may cause damage to the gastric mucosa, manifesting itself by hematemesis.[44] Therefore, when-

44. Durlacher, S. H.; Harrison, W., Jr., and Darrow, B. C.: The Effect of Calcium Chloride and of Calcium Lactate Administered by Gavage, Yale J. Biol. & Med. **18**:135, 1946.

ever possible, calcium salts were administered diluted with milk formula. When food was withheld, 10 per cent calcium chloride solution diluted fivefold with isotonic solution of sodium chloride was given without any evidence of deleterious effect.

Replacement of Potassium and Phosphorus.—In view of the losses of potassium and phosphorus during the acidotic period and their low level in the plasma in the postacidotic period, administration of these ions to the infant with diarrhea appears indicated. The need for potassium and phosphorus may be increased by the administration of large amounts of dextrose with consequent lowering of the plasma level of the ions and their deposition in the liver with glycogen.[45] Several years ago mixtures of potassium and sodium phosphate were administered to patients in diabetic coma and infants with diarrhea, possibly with beneficial results.[5b] Recently, renewed attention has been focused on the losses of potassium during diarrhea and early replacement of the losses has been advocated.[46] The addition of potassium to the armamentarium of fluid therapy appeared to result in a great improvement of the mortality rate of infants from diarrhea. As may be seen from the tables, some of the patients in this series received potassium chloride and phosphate. Although no definite clinical effect aside from changes in the electrocardiogram attended the administration of these ions, it appears reasonable that replacement of all depleted constituents to the infant with diarrhea should have a beneficial result.

SUMMARY

In infants with diarrhea, low levels of calcium, potassium, phosphorus and phosphatase were found in the period following cessation of acidosis and dehydration. The reduction of the ions is thought to be caused by their avid uptake by the previously depleted tissues of the body.

The postacidotic phase of diarrhea is characterized by a clinical picture consisting of lethargy or irritability, convulsions, respiratory embarrassment, derangements of cardiac function, intracranial and gastrointestinal hemorrhages and generalized edema. Less often classic signs of peripheral tetany, carpopedal and laryngeal spasms, are seen. The clinical manifestations appear related primarily to the hypocalcemia, although possible effects of low values of potassium and

45. Fenn, W. O.: The Deposition of Potassium and Phosphate with Glycogen in Rat Livers, J. Biol. Chem. **128**:297, 1939. Flock, E.; Bollman, J. L.; Mann, F. C., and Kendall, E. C.: The Effect of the Intravenous Injection of Glucose and Other Substances on the Concentration of Potassium in the Serum of the Dog, ibid. **125**:57, 1938.

46. Darrow, D. C.: The Retention of Electrolyte During Recovery from Severe Dehydration Due to Diarrhea, J. Pediat. **28**:515, 1946. Govan, C. D., Jr., and Darrow, D. C.: The Use of Potassium Chloride in the Treatment of the Dehydration of Diarrhea in Infants, ibid. **28**:541, 1946.

phosphorus in the plasma cannot be gainsaid. Prematurity, malnutrition, severe diarrhea and acidosis of long duration, considerable fever, extensive dehydration and retention of waste nitrogen favor the occurrence of severe degrees of postacidotic manifestations and hypocalcemia. Correction of the acidosis by alkalizing agents may accentuate the tendency to the postacidotic disturbance. Calcium salts have been of benefit in preventing or curing the postacidotic phase of diarrhea.

CASES ILLUSTRATIVE OF SEVERE MANIFESTATIONS OF THE POSTACIDOTIC STATE

GROUP A, ILLUSTRATIVE OF CONVULSIONS

CASE 1.—H. H., a 1 month old infant, was admitted to the Cincinnati General Hospital on July 19, 1943 with a history of having been undernourished since birth and having recently contracted diarrhea. Examination revealed an acutely ill infant weighing 2,200 Gm. who was extremely dehydrated and malnourished and who was gasping for breath. The turgor of the tissues was poor. On the day of admission the hemoglobin was 10 Gm. per hundred cubic centimeters, the white cell count 33,600, the carbon dioxide 6.7 milliequivalents per liter and the calcium 10.2 mg. per hundred cubic centimeters of plasma. On admission to the hospital continuous intravenous infusions were started, and 1.6 Gm. of sodium bicarbonate was given intravenously, followed by 100 cc. of 5 per cent dextrose in isotonic solution of sodium chloride. Sulfathiazole therapy was also initiated. During the next day he received an additional 200 cc. of salt-containing fluids, 25 cc. of plasma and 50 cc. of blood. On the second day in the hospital mottled cyanosis, abdominal distention, rapid respiration, nystagmus and carpopedal spasm developed, culminating in generalized convulsions. The carbon dioxide in the plasma at that time was 17.5 milliequivalents per liter, the calcium was 5.6 mg. and the phosphorus 4.0 mg. per hundred cubic centimeters. After the administration of 10 cc. of 10 per cent calcium gluconate the patient appeared temporarily improved. Cyanosis and abdominal distention appeared diminished, and the respirations were easier. On the following day his condition grew worse again, the respirations became irregular, and he died suddenly in respiratory arrest. His diarrhea had considerably diminished during his hospital stay. The necropsy revealed congestion of lungs and abdominal viscera, lobular pneumonia and acute enteritis.

CASE 4 *(also presenting bradycardia, and illustrating effect of overdosage of calcium).*—M. W., a 1 month old baby, was admitted to the Cincinnati General Hospital on Aug. 11, 1943 with a history of diarrhea of one week's duration, during which time his stools had become green and watery and had increased in number to about twelve per day. They had not been bloody. Examination revealed a dehydrated, emaciated and cyanotic infant. His hemoglobin on admission was 18.5 Gm. per hundred cubic centimeters; the white cell count was 37,100 and the carbon dioxide in the plasma was 5.4 milliequivalents per liter. The infant was immediately given 100 cc. of isotonic solution of sodium chloride intravenously, followed by 3 Gm. of sodium bicarbonate. He also received 50 cc. of plasma and 300 cc. of 5 per cent dextrose in isotonic solution of sodium chloride. Sulfathiazole therapy was started. Ten hours after admission twitchings of the extremities were noticeable, and the skin was warm and dry. His temperature had risen to 101 F. and rose soon thereafter to 104 F. He appeared cyanotic, his respirations were labored, his body was rigid and his abdomen distended and hard. He began to

convulse and continued to do so for eight hours. A black stool was passed at that time. Bradycardia (a pulse rate of 84 per minute) was noted. The examination of a blood sample drawn showed the carbon dioxide content of the plasma to be 19.4 milliequivalents per liter and the calcium content 6 mg. per hundred cubic centimeters. After the injection of 10 cc. of 10 per cent solution of calcium gluconate his convulsions ceased. Although the diarrhea had greatly diminished within a few hours after admission, he did not continue to improve during the following day. He was given dextrose water by mouth supplemented by small parenteral infusions of blood, plasma and isotonic solution of sodium chloride. He did not take the feedings well and continued to regurgitate them. Lethargy and emesis increased, and intravenous therapy was again instituted. He appeared weak and cyanotic throughout his stay in the hospital and required oxygen inhalation. He began to convulse again on the sixth hospital day and, when an injection of 10 cc. of 10 per cent calcium gluconate was given, sudden cardiac arrest occurred. A blood sample obtained post mortem showed a carbon dioxide content of the plasma of 32.2 milliequivalents per liter and a calcium content of 26 mg. per hundred cubic centimeters of plasma. Two cultures of stools proved negative for pathogens.

CASE 5 *(also illustrating a prompt effect of the calcium therapy).*—G. U., a 4 month old infant, was admitted to the Cincinnati General Hospital on Aug. 3, 1945. The patient had been well until two weeks previously, when diarrhea developed and steadily increased in severity. Examination revealed an extremely dehydrated acutely ill infant who was breathing rapidly. The hemoglobin was 13.5 Gm. per hundred cubic centimeters, there were 16,200 white blood cells and the carbon dioxide content of the plasma was 7.8 milliequivalents per liter. The patient immediately received 1.8 Gm. of sodium bicarbonate and intravenous therapy was instituted, and was continued for four days. Sulfadiazine medication was also begun. Diarrheal stools ceased entirely after admission to the hospital. On the second day in the hospital the child's hydration was greatly improved. In the evening generalized clonic contractions of his extremities developed, associated with nystagmoid movements of his eyes and spasmodic respirations. A blood sample drawn at that time showed a carbon dioxide content of the plasma of 25.1 and a chloride content of 100.8 milliequivalents per liter and a calcium content of 6.2 mg. per hundred cubic centimeters. Two grams of calcium chloride was immediately administered by gavage, and twenty-five minutes later the clonic tremors of the limbs had subsided. Three hours later respirations became labored again, and nystagmoid movements of the eyes and clonic ones of the muscles reappeared. Again 2 Gm. of calcium chloride was administered, and all signs subsided. After this episode he was maintained on calcium chloride therapy in a dosage of 3 Gm. daily for a period of five days. He was discharged well on Aug. 13, 1945. Cultures of stools were negative for pathogens.

CASE 12 *(also presenting hematemesis and edema).*—R. W., a 3 month old infant, was admitted to the Cincinnati Children's Hospital on Aug. 28, 1945 with a history of diarrhea of three weeks' duration and vomiting for the last three days. On admission the patient appeared to be severely dehydrated and undernourished. The temperature was 100 F. The carbon dioxide content of the plasma was 7.8 milliequivalents per liter. He was given immediately an infusion of 1.8 Gm. of sodium bicarbonate, after which a continuous venoclysis was instituted. Sulfadiazine was also given. His diarrhea ceased entirely within the first twelve hours. On the second day in the hospital the child appeared edematous and cyanotic and began to vomit large amounts of bloody material. In the afternoon

clonic movements of the entire body developed and the respirations became more labored. The abdomen was considerably distended and cyanosis had increased. Chvostek's sign was positive. Examination of a sample of blood drawn at that time showed a carbon dioxide content of the plasma of 14.8 milliequivalents per liter, 7.9 mg. of calcium and 19 mg. of nonprotein nitrogen per hundred cubic centimeters. The patient was given 2 Gm. of calcium chloride by oral gavage. Forty minutes later the clonic movements ceased, his respirations became easier and the abdominal distention decreased. Eight hours later the infant again became rigid, and another 2 Gm. of calcium chloride was administered. His respirations during the next two days continued to be irregular and shallow and his cyanosis persisted. On the fourth day in the hospital 1.9 Gm. of sodium bicarbonate was administered because of the clinical impression of acidosis, and a few minutes later the patient suddenly ceased to breathe.

CASE 30.—M. H., a 9 month old infant, was admitted on March 6, 1945 to the Cincinnati Children's Hospital with a history of three days' diarrhea. She had as many as twenty stools daily, which did not contain blood. The examination revealed a poorly nourished and poorly developed child with severe dehydration. The abdomen was scaphoid. The temperature was 103 F. Her hemoglobin was 9.1 Gm. per hundred cubic centimeters, her white cell count 6,400; the carbon dioxide content of the plasma was 7.1, the chloride 145.2 and the sodium 170.6 milliequivalents per liter; the phosphorus was 7.8 and the nonprotein nitrogen 85 mg. per hundred cubic centimeters. The patient received immediately 5 Gm. of sodium bicarbonate followed by 200 cc. of 5 per cent dextrose in isotonic solution of sodium chloride and 1,200 cc. of 5 per cent dextrose in water during eighteen hours of intravenous administration of fluid. Within the first eight hours after admission her temperature rose to 106 F. It dropped to a normal value within another twenty-four hours. Four hours after sodium bicarbonate had been administered, another blood sample showed 24.3 milliequivalents of carbon dioxide and 114.8 of chloride per liter of plasma. The calcium was 5.8 mg. per hundred cubic centimeters and the potassium 2.7 milliequivalents per liter. Six hours later generalized convulsions developed, which subsided after administration of large amounts of phenobarbital sodium. Another twelve hours later—that is, twenty-four hours after admission—the patient was still irritable and had a positive Chvostek's sign. A blood sample drawn at that time showed a plasma p_H of 7.48, 29.4 milliequivalents of carbon dioxide, 106 of chloride and 140.1 of sodium per liter. There was 7.7 mg. of calcium, 3.7 mg. of phosphorus and 35 mg. of nonprotein nitrogen per hundred cubic centimeters. There was 4.2 milliequivalents of potassium per liter. On lumbar puncture a clear spinal fluid with a protein content of 8 mg. per hundred cubic centimeters was obtained. Diarrhea had been absent from the time of admission. Calcium chloride therapy was instituted in a dosage of 3 Gm. daily for a period of two days. She continued to do well and was discharged on March 13, 1945. A blood sample one day before discharge showed 23.3 milliequivalents of carbon dioxide and 143.4 of sodium per liter and 9.5 mg. of calcium per hundred cubic centimeters of plasma.

CASE 42 *(also presenting laryngeal stridor, edema and intracranial bleeding).*—J. E., an 8 month old infant, was admitted to the Cincinnati Children's Hospital on June 22, 1945 with a history of nine days' diarrhea of increasing severity. On the day of admission she suddenly suffered a collapse and was brought to the hospital in a moribund condition. She was admitted in respiratory arrest. Femoral pulse could not be felt, cyanosis was extreme and the temperature was 104.2 F. She was resuscitated and given continuous intravenous infusions for a period of

five days. On the day of admission the hemoglobin was 12.2 Gm. per hundred cubic centimeters, the white cell count 16,300, the plasma p_H 7.20, the carbon dioxide 14.0 and the chloride 104.8 milliequivalents per liter, and the serum protein 4.3 Gm. per hundred cubic centimeters. In the first twenty-four hours the patient remained in a deep coma. The diarrhea diminished during that time and ceased entirely on the second day. On the third day it was noted that internal strabismus of the left eye and lateral nystagmus had developed. The respirations were abdominal and sighing, the extremities were cyanotic and the temperature, which had returned to normal, rose again to 103 F. During the next two days her condition became worse. Her breathing became uneven, and high-pitched respiratory noises were heard. The child continued to have mild convulsive seizures. Pronounced edema developed. A blood sample at that time showed that the plasma contained 25.7 milliequivalents of carbon dioxide, 107.2 of chloride and 141.4 of sodium per liter. The calcium was 7.6 mg., the phosphorus 1.9 mg. and the nonprotein nitrogen 25 mg. per hundred cubic centimeters. The serum protein was 4.4 Gm. per hundred cubic centimeters. An examination of the spinal fluid showed it to be of yellow color with an elevated protein content of 570 mg. per hundred cubic centimeters. She continued in a convulsant state with irregular respirations and increasing edema despite administration of 280 cc. of plasma. On the seventh day in the hospital the p_H of the plasma was 7.46; the carbon dioxide was 18.3, the chloride 104.0 and the sodium 145.4 milliequivalents per liter, and the calcium was 8.6 mg., the phosphorus 2 mg. and the nonprotein nitrogen 25 mg. per hundred cubic centimeters. The spinal fluid at that time was only faintly yellow and contained 54 mg. of protein per hundred cubic centimeters. On that day therapy with calcium chloride in a dosage of 3 Gm. daily was started for a period of five days. The edema disappeared within four days, and her weight decreased from 9,700 to 8,500 Gm. The respirations became more even and her physical condition in general improved. However, the patient remained lethargic and spastic and the strabismus did not disappear. She was discharged, physically improved but with signs of cerebral damage, on July 20, 1945. Her stools were positive for Proteus morganii.

CASE 47.—E. B., a 6 month old infant, was admitted to the Cincinnati Children's Hospital on July 22, 1945 with a history of diarrhea of six days' duration. He had numerous green liquid stools, some of which contained blood and mucus. Examination revealed a fairly well developed, poorly nourished boy who appeared moderately dehydrated. The skin was dry, inelastic, pale and hot. The hemoglobin was 8.8 Gm. per hundred cubic centimeters and the white cell count 21,100. The carbon dioxide in the plasma was 11.9 and the chloride 95.8 milliequivalents per liter, and the calcium 10.8 mg. and the serum protein 6.6 Gm. per hundred cubic centimeters. He received 1.8 Gm. of sodium bicarbonate followed by 400 cc. of dextrose in isotonic solution of sodium chloride and 220 cc. of plasma. About twenty hours after admission the patient suddenly went into circulatory collapse. He became cyanotic, and his respirations were labored. His eyes showed nystagmoid movements, and he shook his arms and legs. A blood sample drawn at that time showed 21.7 milliequivalents of carbon dioxide and 112.7 of chloride per liter of plasma and 6.6 mg. of calcium and 5.4 Gm. of protein per hundred cubic centimeters. Medication with calcium chloride in 3 Gm. dosage was begun, which he received for five days. His improvement was rather slow. On the fourth day in the hospital, when he was still somewhat irritable and lethargic, the carbon dioxide was found to be 26.3

and the chloride 95.6 milliequivalents per liter of plasma and the calcium 9 mg. per hundred cubic centimeters. He was discharged well on Aug. 11, 1945. The spinal fluid was found to be normal in composition. Four cultures of stools were negative for pathogens.

CASE 52 *(also presenting edema and intracranial bleeding).*—R. J., a 4 month old infant, was admitted to the Cincinnati Children's Hospital on Oct. 24, 1944 with a history of diarrhea of five days' duration. Two months previously the baby had been in the hospital for nine weeks, from August 27 to October 10, with severe malnutrition and diarrhea. His spinal fluid at that time was found to be normal on repeated examination. On his second admission he appeared severely dehydrated and emaciated; his eyes were dull and the temperature was 106 F. The hemoglobin was 10.5 Gm. per hundred cubic centimeters and the white cell count 17,600. The carbon dioxide in the plasma was 7.7 milliequivalents per liter and the serum protein was 4.9 Gm. per hundred cubic centimeters. He received 3.5 Gm. of sodium bicarbonate intravenously followed by alternating infusions of 5 per cent dextrose in istonic solution of sodium chloride and 5 per cent dextrose in water. He also received 100 cc. of plasma and 50 cc. of whole blood. Medication with sulfathiazole was instituted. On the following day the the carbon dioxide in the plasma had risen to 20.8 milliequivalents per liter and his temperature had returned to normal. His diarrhea diminished, and on the third day oral feedings of skimmed milk formula were begun. On the fourth day he appeared edematous, pale and stiff. His weight had increased from 4,100 to 5,000 Gm. and his temperature had risen from normal to 101 F. That evening convulsions developed. A blood sample at the time showed 26.7 milliequivalents of carbon dioxide per liter of plasma, and there was 6 mg. of calcium, 2.5 mg. of phosphorus and 4.6 Gm. of serum protein per hundred cubic centimeters. Examination of the spinal fluid revealed blood-tinged fluid under increased pressure, which contained 470 mg. of protein per hundred cubic centimeters and 126 milliequivalents of chloride. A transfusion of citrated blood two hours later was followed by respiratory arrest with cyanosis. Artificial respiration and administration of oxygen and stimulants were successful in resuscitating the infant. Calcium chloride therapy in a dosage of 3 Gm. daily was begun and continued for two days. Within a few hours the child's condition improved greatly, although the convulsive tendency persisted for another day. A blood sample four days after calcium chloride therapy had been initiated showed a plasma p_H of 7.44, 20.2 milliequivalents of carbon dioxide per liter, 7.9 mg. of calcium and 5.8 Gm. of protein per hundred cubic centimeters of serum. His edema had subsided, his weight had decreased to 4,200 Gm. and his temperature was normal. Xanthochromic spinal fluid, which contained 152 mg. of protein per hundred cubic centimeters, was obtained on that day. He continued to do well physically. Another blood sample three days later showed normal plasma p_H and carbon dioxide, 9.6 mg. of calcium and 5.6 Gm. of protein per hundred cubic centimeters of serum. The patient continued to have spasticity of the left arm, showed hypoactive deep reflexes and paid little attention to his surroundings. He was discharged on Nov. 6, 1944, physically recovered but with obvious cerebral damage. Two cultures of stool were negative for pathogens.

GROUP B, ILLUSTRATIVE OF CARPOPEDAL SPASMS

CASE 3 *(also presenting edema).*—C. P., a 1 month old infant, was admitted to the Cincinnati Children's Hospital on Aug. 19, 1945. Three days previously fever and diarrhea had developed, with fifteen watery, green stools daily. On

admission the child appeared critically ill, the respirations were rapid and deep, and the skin appeared gray in color and considerably dehydrated. The temperature was 100 F. The hemoglobin was 9.2 Gm. per hundred cubic centimeters and the white cell count was 7,900. The carbon dioxide was 6.3, the chloride 123.9 and the sodium 142 milliequivalents per liter, and the calcium was 9.8 and the nonprotein nitrogen 37 mg. per hundred cubic centimeters of plasma. The patient was treated with sulfadiazine and intravenous injection of fluids. The administration of 2.2 Gm. of sodium bicarbonate was followed by 250 cc. of dextrose in isotonic solution of sodium chloride. The next day 75 cc. of plasma and the following day 90 cc. of blood in addition to crystalloid solutions were administered. His diarrhea stopped within one day. On the second day in the hospital he appeared edematous and a temperature of 103 F. suddenly developed. He became irritable and had pronounced carpopedal spasms. The Chvostek sign was positive. His skin appeared extremely flushed. A blood sample drawn at that time showed 25 milliequivalents of carbon dioxide and 106.8 of chloride per liter and 6 mg. of calcium and 17 mg. of nonprotein nitrogen per hundred cubic centimeters of plasma. Calcium chloride therapy in a dosage of 3 Gm. daily was given for a period of three days, during which time all signs of spasticity, irritability and edema disappeared. He was discharged in good health on Aug. 29, 1945. Three cultures of stool were negative for pathogens.

GROUP C, ILLUSTRATIVE OF HEMORRHAGIC MANIFESTATIONS

CASE 38 (*presenting hematuria and at necropsy thrombosis of cerebral veins*).—A. S., a 7 month old infant, had been well until two weeks prior to admission. At that time diarrhea developed, which became increasingly severe. About one week before admission he began to vomit. He was admitted to the Cincinnati Children's Hospital on June 25, 1945. The examination revealed a severely dehydrated, acutely ill infant. The fontanel was sunken and the skin was gray and showed mottled cyanosis. The hemoglobin was 6.3 Gm. per hundred cubic centimeters and the white cell count was 5,200. The carbon dioxide was 21.2 and the chloride 84.4 milliequivalents per liter of plasma; the calcium was 8.6 mg. per hundred cubic centimeters and the serum protein 5.7 Gm. He was placed on continuous intravenous therapy, which he received until his death four days later. He received daily a total of 750 to 1,000 cc. of fluids, of which 150 to 500 cc. was salt-containing. His daily parenteral intake of protein ranged from 5 to 40 Gm. In the first three days he was given 250 cc. of plasma daily, as well as several transfusions of blood. He was placed on both penicillin and sulfadiazine therapy. His diarrhea continued for the first two days in the hospital. On the third day oral feedings were instituted. During that time repeated examinations of the blood showed normal values for carbon dioxide, chloride and nonprotein nitrogen. On the fourth day he appeared somewhat improved, but in the evening he suddenly became much more ill and lethargic and had rapid and shallow respirations with periods of apnea. His abdomen became increasingly distended. Nystagmus and strabismus were noted. A blood sample drawn at that time revealed a plasma p_H of 7.48, 29.2 milliequivalents of carbon dioxide and 116 of chloride per liter, 5.8 mg. of calcium and 4.6 Gm. of serum protein per hundred cubic centimeters. The sodium was 160.6 milliequivalents per liter. A few hours before death urticaria-like lesions of the abdomen developed, and he later became cyanotic. Shortly before death he passed bloody urine. Important abnormalities noted at necropsy were limited to the brain. The brain appeared to be injected, and two cerebral vessels in the anterior portion were found to be thrombosed. Microscopic sections

revealed acute passive congestion of veins, edema in the brain and focal areas of hemorrhage around thrombosed small veins.

CASE 49 (*presenting hematemesis*).—M. C., a 2 month old premature infant, was admitted to the Cincinnati Children's Hospital on Aug. 17, 1945 with a history of vomiting all feedings for a week and of diarrhea for three days. The infant appeared emaciated and severely dehydrated. The hemoglobin was 5.9 Gm. per hundred cubic centimeters and the white cell count 18,400. The carbon dioxide in the plasma was 10.5 and the chloride 101.6 milliequivalents per liter; the calcium was 7.7 and the nonprotein nitrogen 72 mg. per hundred cubic centimeters. The patient received immediately 1 Gm. of sodium bicarbonate and was given a continuous intravenous infusion for a period of two days. Therapy with sulfadiazine was begun. In the first few hours her condition appeared grave. She vomited at first clear and later bloody fluid and her respirations were labored. No stools were passed. A blood sample ten hours after admission showed 13 milliequivalents of carbon dioxide and 101.3 of chloride per liter of plasma and 7.4 mg. of calcium, 46 mg. of nonprotein nitrogen and 2.6 mg. of phosphorus per hundred cubic centimeters. There was 5.4 Gm. of protein per hundred cubic centimeters of serum. Calcium chloride therapy in a dosage of 2 Gm. daily was begun and continued for four days. A blood sample on the tenth day in the hospital showed 19.4 milliequivalents of carbon dioxide per liter and 9.1 mg. of calcium, 5.2 mg. of phosphorus and 5.8 Gm. of protein per hundred cubic centimeters of serum. She was discharged well on Sept. 7, 1945.

GROUP D, ILLUSTRATIVE OF BRADYCARDIA AND SYSTOLIC MURMURS

CASE 53 (*also presenting laryngeal stridor, fever and cerebral hemorrhage*).—T. F., a 1 month old infant, was admitted to the Cincinnati General Hospital on Nov. 23, 1944 with a history of diarrhea and vomiting for one day. Examination revealed a small, fairly well developed infant who was pale and lethargic. Dehydration was marked, and his temperature was 100 F. The hemoglobin was 16.5 Gm. per hundred cubic centimeters and the white cell count 12,600. The carbon dioxide was 12.1 milliequivalents per liter of plasma and the blood urea nitrogen was 24 mg. per hundred cubic centimeters. He was given treatment with sufadiazine and received an infusion of 250 cc. of 5 per cent dextrose in isotonic solution of sodium chloride. On the following day oral feedings of sodium lactate and isotonic solution of three chlorides and 5 per cent dextrose in water were initiated, followed by a formula of skimmed milk on the next day. On the second day in the hospital, when his hydration had improved considerably, his temperature rose to 103 F. The carbon dioxide in his plasma at that time had increased to 16.8 milliequivalents per liter. His diarrhea became worse on the fourth hospital day; the carbon dioxide in the plasma dropped to 12.8 milliequivalents per liter, and the urea nitrogen rose to 42 mg. per hundred cubic centimeters. His temperature was 100 F. Again he received 1 Gm. of sodium bicarbonate, and continuous intravenous administration of fluid, including 200 cc. of plasma, was instituted. On the eighth day in the hospital he appeared edematous and breathed rapidly with a loud respiratory crowing noise. At that time bradycardia (pulse rate of 86) and a systolic murmur were noted. His diarrhea had improved and his temperature had risen to 102 F. A blood sample taken at that time showed that the p_H of the plasma was 7.38, that there were 21.6 milliequivalents of carbon dioxide and 2.5 of potassium per liter and 8.4 mg. of calcium, 1.8 mg. of phosphorus and 5.6 Gm. of serum protein per hundred cubic centimeters. When oral feedings were resumed his diarrhea recurred with renewed vigor, and he became dehydrated again. His temperature dropped

to 99 F. A blood sample on the eleventh day showed a plasma p_H of 7.12, 10.1 milliequivalents of carbon dioxide and 2.3 of potassium per liter, and 11.3 mg. of calcium and 2.1 of phosphorus per hundred cubic centimeters of plasma. The serum protein was 4.7 Gm. per hundred cubic centimeters. One and one-half grams of sodium bicarbonate was administered and continuous intravenous infusions were started. He also received 100 cc. of blood and 100 cc. of plasma. On the following day the carbon dioxide in the plasma had risen to 23 milliequivalents per liter. His condition was slightly improved but he appeared lethargic and was breathing poorly. On that day the baby became increasingly edematous, his abdomen became distended and his skin suddenly became extremely flushed. The temperature rose to 103 F. A blood sample at that time showed a plasma p_H of 7.42, 27.4 milliequivalents of carbon dioxide and 2.1 of potassium per liter, and 7 mg. of calcium, 2.2 mg. of phosphorus and 5.4 Gm. of serum protein per hundred cubic centimeters. The infant's condition worsened steadily; the respirations became shallow and gasping. A small bloody and mucoid stool was passed shortly before death. Necropsy showed a subdural hematoma on the right side, cerebral congestion and edema, and thrombotic occlusions of small cerebral veins. Repeated cultures of stools were negative for pathogens.

CASE 54 *(also presenting hematemesis, edema, strabismus and abdominal distention).*—F. was born at a Cincinnati hospital during an epidemic of diarrhea of the newborn. She was admitted to the Cincinnati Children's Hospital on Nov. 4, 1944, the fourteenth day of her life. On the day before admission she had eighteen liquid stools. The patient appeared small, cyanotic and extremely dehydrated, and was breathing heavily. The tongue was reddened and its tip showed prominent papillae. The carbon dioxide in the plasma on admission was 4.8 milliequivalents per liter and the phosphorus was 6.5 mg. per hundred cubic centimeters. The patient was given sodium bicarbonate to correct the acidosis, and continuous intravenous administration of fluids was begun. A blood sample on the next day showed 12.4 milliequivalents of carbon dioxide per liter of plasma. Hydration of the infant improved and the stools decreased somewhat in frequency. Oral feedings of crystalloid solutions were instituted. During the next several days the patient's diarrhea persisted, and she once more had a low level of carbon dioxide in the plasma, which was corrected by the administration of sodium bicarbonate. By the tenth day her diarrhea had diminished but her condition had become grave. She was extremely edematous and her abdomen was distended. Bloody material was being vomited. The baby was deeply cyanotic and cool to touch. Hands and feet were held in a tightly clenched position. Nystagmus and strabismus were evident. A heart rate of 80 per minute and a loud systolic murmur were noted. An electrocardiogram showed an atrioventricular block and a prolonged Q-T interval with flattened T waves. A blood sample at that time showed a plasma p_H of 7.39, 24.8 milliequivalents of carbon dioxide and 3 of potassium per liter, and 6.8 mg. of calcium and 2.7 mg. of phosphorus per hundred cubic centimeters. During the next two days her condition slightly improved. However, her edema increased. A blood sample at that time showed a plasma p_H of 7.50, 30.1 milliequivalents of carbon dioxide and 3.6 of potassium per liter, and 7.5 mg. of calcium and 1.5 mg. of phosphorus per hundred cubic centimeters. Therapy with calcium gluconate in a dosage of 6 Gm. daily was instituted and continued for a period of five days. Her edema subsided rapidly, and her respirations improved. The pulse rate rose to 120 per minute and the heart murmur disappeared. Coordination of the eyes returned. A blood sample taken after two days of calcium therapy showed 31.1 milliequivalents of carbon dioxide and 6.8 of potassium per liter and 10.2 mg. of calcium

and 4.2 mg. of phosphorus per hundred cubic centimeters. An electrocardiogram at that time was normal in all respects. The child was discharged well on Nov. 28, 1944. Repeated cultures of stools were negative for pathogens.

CASE 55 *(also presenting edema and strabismus).*—T. G., a 16 day old girl, was admitted to the Cincinnati Children's Hospital on Nov. 17, 1944. She had been born in a Cincinnati hospital during an epidemic of diarrhea of the newborn. On admission the infant appeared moderately dehydrated and was breathing rapidly and deeply. The hemoglobin was 8.7 Gm. per hundred cubic centimeters, and the white cell count was 17,600. The carbon dioxide was 6.5 and the potassium 4.4 milliequivalents per liter of plasma; the phosphorus was 6.7 mg. and the nonprotein nitrogen 40 mg. per hundred cubic centimeters. The patient received 2 Gm. of sodium bicarbonate immediately and was given a continuous intravenous infusion for a period of twenty-four hours. She received 70 cc. of plasma, 220 cc. of 5 per cent dextrose in isotonic solution of sodium chloride and 200 cc. of 5 per cent dextrose in water. Therapy with sulfadiazine was also begun. Her diarrhea diminished during the first day. A blood sample at that time showed a plasma p_H of 7.40, 19 milliequivalents of carbon dioxide and 2.9 of potassium per liter and 8.4 mg. of calcium per hundred cubic centimeters. Oral feeding of small amounts of crystalloid solution was attempted. During the next days her diarrhea worsened and she became dehydrated again. A blood sample on the sixth day showed a plasma p_H of 7.22, 11.9 milliequivalents of carbon dioxide and 3.5 of potassium per liter and 10.3 mg. of calcium and 4.1 Gm. of serum protein per hundred cubic centimeters. She received 2 Gm. of sodium bicarbonate, 60 cc. of plasma and 85 cc. of 5 per cent dextrose in isotonic solution of sodium chloride. On the following day the carbon dioxide in the plasma had risen only to 12.4 milliequivalents per liter. Again 1.8 Gm. of sodium bicarbonate was administered. The diarrhea began to subside and the baby started to take her formula better but became slightly puffy around the eyes. On the next day her edema had increased considerably and on the following day it had become extreme. On that day strabismus was noted, the pulse rate had decreased to 88 from 160 per minute and a soft systolic murmur was heard. A blood sample showed a plasma p_H of 7.41, 23.1 milliequivalents of carbon dioxide and 5.1 of potassium per liter and 8 mg. of calcium, 3.2 mg. of phosphorus and 4 Gm. of serum protein per hundred cubic centimeters. The patient was placed on therapy with calcium chloride in a dosage of 3 Gm. daily for a period of two days, followed by medication with calcium gluconate in a dosage of 4 Gm. daily for a period of five days. Her edema subsided rapidly and the heart rate and heart sounds became normal. A blood sample taken three days after calcium therapy had been initiated showed a plasma p_H of 7.37 and 19.3 milliequivalents of carbon dioxide and 5.9 of potassium per liter. The calcium was 11.1 mg. and the serum protein 5.2 Gm. per hundred cubic centimeters. She was discharged well on Dec. 8, 1944. Her stools were positive for virus.

GROUP E, INFANTS WHO RECEIVED EXCESSIVE SODIUM LACTATE IN FORMULA

CASE 59 *(presenting edema and fever).*—M. P., a 6 month old infant, was admitted on Nov. 13, 1944 to the Cincinnati Children's Hospital. She had been in good health until five weeks before admission, when mild diarrhea developed which persisted for three weeks. Examination showed a well developed, malnourished infant who appeared severely dehydrated. The skin was dry and inelastic; the temperature was 103 F. The hemoglobin was 12.2 Gm. per hundred cubic

centimeters and the white cell count was 20,600. The p_H of the plasma was 7.30, the carbon dioxide 18.1 milliequivalents per liter, the calcium 10.5 mg. and the serum protein 6.5 Gm. per hundred cubic centimeters. The child was given continuous intravenous therapy. She received 2 Gm. of sodium bicarbonate and 150 cc. of plasma on the first day. Administration of sulfathiazole was also started on admission. The diarrhea diminished considerably on the following day and the infant was given a formula consisting of equal parts of 10 per cent casein hydrolysate, 10 per cent dextrose and sixth-molar sodium lactate. Hydration improved and the child gained more than 500 Gm. in the next two days. The temperature, which had returned to normal, increased on the third day to 101 F. and the patient appeared ill, lethargic and edematous. On that day the carbon dioxide in the plasma had risen to 35.1 milliequivalents per liter, while the calcium had dropped to 7.7 mg. per hundred cubic centimeters. The serum protein was 5.9 Gm. On the next day she appeared worse; her temperature had risen to 103 F.; the p_H of her plasma had increased to 7.66 and the carbon dioxide to 43.6 milliequivalents per liter, while the values for chloride and for potassium were low, 84 and 2.8 milliequivalents per liter. The calcium was 6.3 mg. and the phosphorus 3 mg. per hundred cubic centimeters. A phosphatase activity of 2.3 Bodansky units was measured. After the chemical status of the patient was discovered, the alkali-containing formula was replaced by a standard milk formula and therapy with calcium chloride in a dosage of 3 Gm. daily was started. In the next two days the patient's condition improved considerably, the temperature returned to normal and the lethargy disappeared. A blood sample taken after two days of calcium therapy showed a normal plasma p_H of 7.39, 23.7 milliequivalents of carbon dioxide and 106.4 of chloride per liter. The calcium had risen to 9.1 mg. and the phosphorus to 3.5 mg. per hundred cubic centimeters and the potassium to 6.1 milliequivalents per liter. Another sample three days later, after all medication had been stopped, showed normal values for all constituents; the calcium was 9.3 and the phosphorus 4.1 mg. per hundred cubic centimeters; the potassium was 5.4 milliequivalents per liter and the phosphatase 7.4 Bodansky units. The serum protein was 5.4 Gm. per hundred cubic centimeters. The patient was discharged well on Dec. 4, 1944.

CASE 61 *(presenting bradycardia and systolic murmur, edema, cyanosis and strabismus).*—E. P., a 2 month old premature twin, was admitted to the Cincinnati Children's Hospital on Nov. 3, 1944 with a history of diarrhea of three days' duration. Examination revealed a well developed premature infant who was only moderately dehydrated. The hemoglobin was 8.8 Gm. per hundred cubic centimeters and the white cell count was 8,200. The carbon dioxide was 17.7 milliequivalents per liter, and the nonprotein nitrogen 30 mg. per hundred cubic centers of plasma. She received 150 cc. of salt-containing fluids parenterally and, since the diarrhea was mild, she was placed on oral feedings. On the sixth hospital day the diarrhea became worse and the feedings were supplemented with fluids given parenterally. On that day the carbon dioxide was 17.8 milliequivalents per liter. She was placed on a formula consisting of equal parts of 10 per cent dextrose, 10 per cent casein hydrolysate and sixth-molar sodium lactate. Diarrhea diminished, but edema began to develop rapidly. Administration of 110 cc. of blood and 125 cc. of plasma failed to affect the edema, and her weight increased from 2,600 to 3,300 Gm. She became increasingly pale, and on the fourth day of receiving the alkali-containing formula she suddenly suffered a cyanotic spell with temporary respiratory arrest. Bradycardia developed (30 to 40 beats per minute) and a loud harsh systolic murmur. Strabismus was noted. Her temperature had increased

from normal to 100 F. A blood sample drawn at that time revealed a plasma p_H of 7.58, 43.2 milliequivalents of carbon dioxide, 93.6 of chloride and 2.6 of potassium per liter, and 8.4 mg. of calcium and 4.8 Gm. of serum protein per hundred cubic centimeters. When the alkalotic condition of the infant was realized, calcium chloride therapy was instituted in a dosage of 3 Gm. daily for a period of two days. She became more alert, the heart murmur became much fainter and the heart rate returned to normal. Her weight decreased to 2,600 Gm. A blood sample drawn after the two day period of calcium therapy showed that the p_H of the plasma had returned to 7.43, that the carbon dioxide was 30.1 milliequivalents per liter, the calcium 11.7 mg. per hundred cubic centimeters and the potassium 6.6 milliequivalents per liter. The serum protein was 5.1 Gm. per hundred cubic centimeters. During the next few days the heart murmur disappeared entirely and she continued to do well. Another blood sample showed normal values for calcium and potassium. She was discharged on Nov. 26, 1944 in apparent good health. Two cultures of stools were negative for pathogens.

FEEDING OF PREMATURE INFANTS

A Comparison of Human and Cow's Milk

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HUMAN milk is widely regarded as the food of choice for premature infants. Recently summarized laboratory investigations [1] have cast doubt on this widely held clinical impression. To reassess the problem, carefully controlled clinical studies were undertaken comparing the progress of premature infants fed isocaloric amounts of human milk or mixtures of cow's milk under comparable conditions of nursing, medical and environmental conditions. The present report compares the gains in weight of 122 premature infants whose weights at birth were between 1,000 and 2,000 grams (2 pounds, 3 ounces and 4 pounds, 6 ounces), all of whom were fed isocaloric amounts of either human milk, a simple mixture of evaporated milk or a mixture of partially skimmed cow's milk. The results indicate that greater gains in weight were achieved with the mixture of partially skimmed milk [2] than with evaporated milk, and that both mixtures of cow's milk were superior to human milk, particularly for smaller infants. In addition, data will be presented for 14 infants who weighed less than 1,000 Gm. (2 pounds, 3 ounces) on admission to the nurseries and who gained weight satisfactorily on mixtures of partially skimmed milk. These infants were not included in the statistical analysis.

SUBJECTS AND METHODS

The subjects were all healthy, prematurely born infants. Most of the infants were born in the New York Hospital, a few infants being transferred from other hospitals.

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The United States Children's Bureau gave assistance in the collection of the material on which this study is based. The analysis of the data was made by the authors.

1. Gordon, H. H., and Levine, S. Z.: The Metabolic Basis for the Individualized Feeding of Infants, Premature and Full Term, J. Pediat. **25**:464, 1944.

2. Powers, G. F.: Comparison and Interpretation on a Caloric Basis of the Milk Mixtures Used in Infant Feeding, Am. J. Dis. Child. **30**:453 (Oct.) 1925.

All infants resided in an air-conditioned nursery, maintained at a constant environmental temperature and a relative humidity of 77 F. and 65 per cent, respectively.[3] Infants who weighed less than 1,500 Gm. and larger ones who required oxygen therapy were kept in incubators at high oxygen concentrations, high humidity and environmental temperatures above 77 F. Vitamin K was given routinely to all infants on admission and sulfonamide drugs or penicillin was used freely in prophylaxis during the first week for infants who were doing poorly.[4]

The routine feeding schedule consisted of (*a*) a fasting period for all infants for twelve hours after birth; (*b*) for infants below or above 1,500 Gm., 8 or 15 cc. of 5 per cent solution of dextrose, respectively, every three hours for the next twelve hours; (*c*) 15 or 30 cc. of equal parts of 5 per cent solution of dextrose and the chosen feeding mixture every three hours for the next twelve hours, and (*d*) 15 or 30 cc. of the feeding mixture every three hours thereafter, the amounts being adjusted for individual infants according to size and ability to ingest and retain the offered amounts.

By the end of the first week of life all infants were receiving mixtures of 120 calories per kilogram per twenty-four hours,[5] and this level was maintained by adjustments in relation to weight every three or four days. Ascorbic acid was given daily to all infants, beginning by the fourth or the fifth day, and concentrates of vitamins A and D by the seventh day of life.

Gavage feedings were used whenever the infant was unable to ingest the prescribed intake from nipple or medicine dropper. Liberal use of this procedure was possible because an adequate number of trained nurses under expert supervision was available. Close medical supervision was provided by the pediatric resident, an assistant resident and the intern assigned to the nurseries for premature infants.

Details of the three feeding mixtures are presented in table 1. The human milk was obtained from two sources: mothers of infants born in the New York Hospital and the Mother's Milk Bureau of the Children's Welfare Federation. The milk obtained at the New York Hospital was pooled daily, boiled for five minutes with stirring in an open pan, strained to remove coagulum and apportioned in the formula room to supply the

3. Blackfan, K., and Yaglou, C. P.: The Premature Infant: A Study of the Effects of Atmospheric Conditions on Growth and on Development, Am. J. Dis. Child. **46**:1175 (Nov., pt. 2) 1933.

4. Gordon, H. H.: Reducing the Hazards of the First Two Days of Life for Premature Infants: Round Table Discussion, J. Pediat. **23**:471, 1943.

5. Gordon, H. H.; Levine, S. Z.; Deamer, W. C., and McNamara, H.: Respiratory Metabolism in Infancy and in Childhood: XXIII. Daily Energy Requirements of Premature Infants, Am. J. Dis. Child. **59**:1185 (June) 1940.

daily needs of the infants. Any excess milk was frozen and stored in an apparatus provided by the Mother's Milk Bureau.[6] When the hospital supply of milk was inadequate, milk was bought from the Mother's Milk Bureau. This milk represented a pooling from a larger number of mothers than in the hospital. It was delivered to the hospital as fresh or frozen pasteurized milk and was also boiled five minutes prior to use.

The mixtures of cow's milk were dilutions of either evaporated milk or powdered partially skimmed milk reenforced with Dextri-Maltose. It is seen in table 1 that feeding mixture A (human milk) was low in protein and high in fat and fluid as compared with the mixtures of cow's milk, B and C. The chief difference between B and C was in the lower fat content of the latter. Both mixtures of cow's milk contained greater

TABLE 1.—*Feeding Mixtures Designed to Give One Hundred and Twenty Calories per Kilogram (Fifty-Five Calories per Pound)*

			Gm./Kg.			Percentage of Total Calories		
	Per Kg.	Per Lb.	Protein	Fat	Carbohydrate	Protein	Fat	Carbohydrate
A. Human milk	180 cc.	2½ oz.	2.2	6.7	12.9	7	50	43
B. Evaporated milk	70 cc.	1 oz.	4.8	5.5	12.9	16	41	43
Carbohydrate	6 Gm.	3 Gm.						
Water to make	150 cc.	2¼ oz.						
C. Half-skimmed milk powder	18 Gm.	1 T.*	6.0	2.2	19.4	20	16	64
Carbohydrate	11 Gm.	5 Gm.						
Water to make	150 cc.	2¼ oz.						

* T = tablespoonful.

amounts of calcium, phosphorus and other minerals than did the human milk. Comparison of the results of feeding mixtures A and B permits an estimate of the desirability of high protein and mineral intakes; comparison of B and C, of the importance of low fat intakes.

For the infants under 1,000 Gm., the water added to the powdered partially skimmed milk was sometimes less than that shown in table 1, since a previous study indicated that 120 cc. of fluid per kilogram was adequate to cover the infants' requirements under the environmental conditions of the study. As increasing vigor permitted ingestion of larger amounts of fluid, the intake was increased to customary levels of 150 cc. per kilogram.[7] As previously stated, these infants were not included in the statistical study.

6. The Mother's Milk Bureau gave cordial cooperation, which facilitated efficient utilization of the hospital milk supply.

7. Gordon, H. H.; Levine, S. Z.; McNamara, H.; Marples, E., and Benjamin, H. R.: Respiratory Metabolism in Infancy and in Childhood: XXIV. Daily Water Exchange of Premature Infants, Am. J. Dis. Child. **61**:524 (March) 1941.

MATERIAL STUDIED STATISTICALLY

Eighty-eight infants were fed one of the three feeding mixtures according to a prearranged schedule of rotation based on sex, weight at birth, plurality of birth and race. This was done because preliminary analyses of the feeding records at the New York Hospital of 530 premature infants for the third week of life indicated that male infants gained more rapidly than female infants regardless of the type of feeding.[8] Because the degree of immaturity might be expected to affect the storage and digestive handicaps which conditioned progress on the respective diets, weight at birth, plurality of birth and race[9] were also used in setting up the rotation system. For example, the first white, female, single-born infant whose weight at birth was between 1,000 and 1,249 Gm. was assigned to mixture A, the second to mixture B and the third to mixture C, with similar rotation for other categories of weight at birth, sex, color and plurality of birth. If an infant died soon after birth, suffered from congenital anomalies or became ill, his record was subsequently discarded from the statistical analysis. A shortage of human milk which developed in the course of the study led to curtailment of the number of infants in this group, so that of the 88 infants fed in rotation only 16 received human milk as compared with 39 for evaporated milk and 33 for half-skimmed milk. At the end of the rotation study, 34 additional infants were fed the last mixture. They are included in the analysis for the reason presented hereafter (table 3).

METHOD OF ANALYSIS OF RESULTS

The mean gain in weight was measured in grams per kilogram per day for a period of twenty-one days, from the seventh to the twenty-eighth day of life. Thus, all infants on the rotated feeding schedule were observed for a minimum of twenty-eight days. No records were analyzed for infants who weighed over 2,000 Gm. at birth, since they rarely stayed in the hospital for twenty-eight days and since the effect of different types of food on gain in weight in this weight group would presumably be less significant than in smaller premature infants. There were so few Negro infants that their records were omitted from analysis. Furthermore, the records of infants who became ill during the period of study were excluded from analysis regardless of the nature of the illness. There were two outbreaks of infectious diarrhea and, as might be expected, babies on all three feeding mixtures were affected.

8. Children's Bureau: Unpublished data.

9. Dunham, E. C.; Jenss, R. M., and Christie, A. U.: A Consideration of Race and Sex in Relation to the Growth and Development of Infants, J. Pediat. **14**:156, 1939.

TABLE 2.—*Mean Daily Gains in Weight, in Grams per Kilogram per Day of One Hundred and Twenty-Two Premature Infants* *

	Below Mean Birth Weight of 1,621 Gm.								Above Mean Birth Weight of 1,621 Gm.							
	Girls				Boys				Girls				Boys			
	Single Births		Multiple Births		Single Births		Multiple Births		Single Births		Multiple Births		Single Births		Multiple Births	
Feedings	Weight Gain	Birth Weight, Gm.	Weight Gain	Birth Weight, Gm.	Weight Gain	Birth Weight, Gm.	Weight Gain	Birth Weight, Gm.	Weight Gain	Birth Weight, Gm.	Weight Gain	Birth Weight, Gm.	Weight Gain	Birth Weight, Gm.	Weight Gain	Birth Weight, Gm.
Rotation schedule																
Human milk	10.1	1,222	—	—	9.7	1,242	—	—	11.6	1,848	11.3	1,638	9.0	1,854	11.4	1,842
	10.8	1,354			15.8	1,362			13.6	1,666	13.7	1,754	11.3	1,706	13.4	1,670
									13.7	1,750			14.4	1,798		
									13.8	1,750			15.5	1,784		
Evaporated milk	10.7	1,610	13.9	1,476	11.1	1,384	—	—	6.1	1,904	12.9	1,782	11.5	1,852	11.6	1,962
	11.7	1,112	14.6	1,478	14.5	1,158			11.1	1,710	13.2	1,802	12.0	1,658	11.7	1,712
	13.8	1,232			16.6	1,398			13.0	1,992	13.4	1,642	13.7	1,838	12.5	1,712
	15.4	1,247			18.2	1,476			13.6	1,864			14.4	1,838	13.0	1,840
	15.5	1,488			20.2	1,514			14.2	1,932			15.0	1,672	13.8	1,930
	15.9	1,572							14.3	1,720			15.1	1,782	17.8	1,812
	16.6	1,250							14.7	1,754			17.9	1,976		
									16.3	1,656						
									19.0	1,676						
Partially skimmed milk	13.1	1,022	16.2	1,440	12.4	1,286	17.6	1,568	8.2	1,774	12.8	1,840	8.7	1,980	13.3	1,770
	15.3	1,198	19.5	1,400	16.0	1,594	18.6	1,478	11.5	1,736	14.3	1,780	9.9	1,750	15.4	1,910
	16.2	1,406			16.8	1,498			13.8	1,906			13.7	1,716		
	17.2	1,517			17.1	1,272			15.1	1,798			15.5	1,884		
	17.5	1,516							15.9	1,730			16.0	1,984		
	19.2	1,088							17.1	1,662						
	20.8	1,176							17.1	1,640						
	21.0	1,148							17.6	1,630						
Not in rotation																
Partially skimmed milk	11.5	1,400	12.5	1,360	15.5	1,247	—	—	15.0	1,700	9.3	1,850	5.6	1,722	16.5	1,930
	15.5	1,370	16.4	1,580	17.3	1,442			15.3	1,752	14.9	1,640	7.9	1,720	16.8	1,810
	16.0	1,600	17.5	1,480	21.4	1,260			16.4	1,950	17.3	1,840	10.0	1,690		
	16.4	1,550			21.5	1,440			16.6	1,690	17.6	1,640	12.2	1,810		
	17.3	1,610											12.6	1,860		
	18.7	1,250											13.8	1,900		
	20.5	1,460											17.6	1,738		
	23.7	1,080											17.8	1,823		
													21.7	1,640		

* All infants were fed 120 calories per kilogram a day. The mean weights were calculated for the period from the seventh to the twenty-eighth day and are expressed as grams per kilogram per day of mean body weight for the period $\left[\frac{W28 - W7}{21\left(\frac{W28 + W7}{2,000}\right)}\right]$.

The reliability of differences between the averages of the mean gains in weight was studied by analysis of variance.[10] A 5 per cent level being used as a criterion of significance, it was found that for this sample the differences in mean gains in weight on the three diets were not significantly larger or smaller between (*a*) girls and boys and (*b*) single-born infants and infants born as twins. Among the infants fed the powdered half-skimmed milk the difference in mean gains in weight between those fed in rotation and those fed not in rotation was not significant, and this

TABLE 3.—*Statistical Significance of Differences*[10b]

	Number of Infants	Comparison	"F" (Variance Ratio)	An "F" (Variance Ratio) as Large or Larger than the One Obtained May Be Expected to Occur by Chance			
				Much More Often Than 5%	More Often Than 5%	Between 1 and 5%	Less Often Than 1%
Rotation	88	Girls and boys	Less than 1.00	+	..	..	..
All	122	Girls and boys	Less than 1.00	+	..	..	..
Rotation	88	Single born and twins	Less than 1.00	+	..	..	..
All	122	Single born and twins	Less than 1.00	+	..	..	..
Half-skimmed milk	67	Rotated and nonrotated	Less than 1.00	+	..	..	..
Whole sample	55	Human and evaporated milk	5.04	..	..	+	..
	106	Half-skimmed and evaporated milk	5.38	..	..	+	..
	83	Half-skimmed and human milk	11.82	..	..	..	+
Lower birth weights	18	Human and evaporated milk	4.55	..	..	+	..
	45	Half-skimmed and evaporated milk	7.14	..	..	+	..
	35	Half-skimmed and human milk	14.01	..	..	..	+
Higher birth weights	37	Human and evaporated milk	1.31	..	+	..	..
	61	Half-skimmed and evaporated milk	Less than 1.00	+	..	..	..
	48	Half-skimmed and human milk	1.94	..	+	..	..

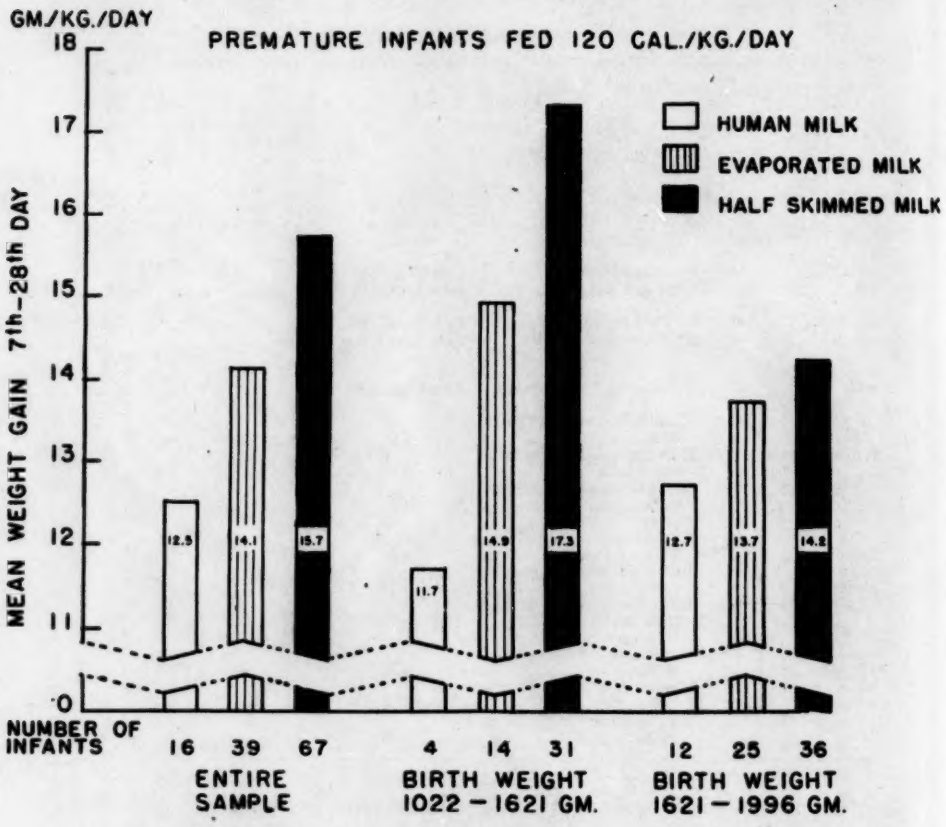
difference was not significantly larger or smaller between (*a*) girls and boys and (*b*) single-born infants and infants born as twins. Accordingly, in the final analysis in this study, no distinction was made between boys and girls, between single-born and twins or between infants fed in the rotation and in the nonrotation studies. The merging of results for the various groups seemed permissable for this study; in setting up similar studies a rotation scheme such as the one used is still indicated.

10. (*a*) All statistical analyses were made by Mr. M. H. Gordon. (*b*) Snedecor, G. W.: Statistical Methods, Ames, Iowa, The Collegiate Press, Inc., 1946.

RESULTS

The detailed results are presented in table 2 and a summary in the figure, all the infants being divided into two groups, those above and those below the mean weight at birth of 1,621 Gm. (3 pounds, 9 ounces) for the whole sample of 122 infants. Table 3 indicates the statistical significance of the differences noted.

For the 16 infants fed human milk, the average gain in weight was 12.5 Gm. per kilogram per day as compared with 14.1 Gm. for the 39



Comparison of mean gains in weight of premature infants

infants fed evaporated milk and 15.7 Gm. for the infants fed half-skimmed milk. The differences were all significant; i. e., those between human and evaporated milk and between evaporated and half-skimmed milk may be expected to occur by chance between only 1 and 5 per cent and between human and half-skimmed milk less than 1 per cent of the time (table 3).

When the groups were subdivided into "smaller" and "larger" infants according to weight at birth, the differences for the former group between

the results on human milk and on the cow's milk diets were larger. For the larger infants, however, differences among the three diets were smaller and not statistically significant.

COMMENT

The results of this statistical study support the laboratory investigations which suggested that mixtures of cow's milk are more suited for the peculiar needs of premature infants than human milk. That part of this superiority is due to the increased protein content of cow's milk is suggested by observations that the addition of calcium paracaseinate [11] and of amino acids [12] to human milk produces greater gains in weight. This may explain why both preparations of cow's milk used in this study were superior to human milk, although the possibility exists that the higher mineral content of cow's milk may have been a factor also. For infants with a defect in absorption of fat, partially skimmed milk is obviously indicated.[13] Although the skimming of human milk is not simple, its use has been recommended.[14] A feeding mixture of partially skimmed milk such as the one in this study has been used successfully by Powers [15] for many years in the routine feeding of premature infants. Added evidence for the value of the latter is presented in table 4, which contains data on 14 infants whose weights on admission to the nursery for premature infants of the New York Hospital were 1,000 Gm. or less. As is seen, all of them gained well on 120 calories of the mixture of half-skimmed milk per kilogram. For 11 of them who were on this feeding from the seventh to the twenty-eighth day of life, the mean gain in weight per day during this period was 17.6 Gm. per kilogram as compared with 17.3 Gm. for the 31 infants in the study whose weights at birth were between 1,000 and 1,621 Gm. According to Streeter [16] the

11. Langer, H.: Ueber die Ernährung frühgeborener Kinder in den ersten Lebenswoche, Ztschr. f. Kinderh. **41**:598, 1926. Poole, M. W., and Cooley, T. B.: The Care of Premature Infants, J. Pediat. **1**:16, 1932.

12. Magnusson, J. H.: Ueber die Anwendung eines Aminosaurengemisches (Kaseinhydrolysat) als Zusatznährung für Frühgeborene wahrend der ersten Lebenswochen, Acta paediat. **32**:599, 1945.

13. Gordon, H. H., and McNamara, H.: Fat Excretion of Premature Infants: I. Effect on Fecal Fat of Decreasing Fat Intake, Am. J. Dis. Child. **62**:328 (Aug.) 1941.

14. Ylppö, A.; Zur Physiologie, Klinik und zum Schicksal der Frühgeborenen, Ztschr. f. Kinderh. **24**:1, 1919. Salge, B.:. Der akute Dünndarmkatarrh des Säuglings, Leipzig, Georg Thieme, 1906; cited by Friedberg, E., and Noegerrath, C.: Entfettete Frauenmilch als Heilnährung, Arch. f. Kinderh. **68**:195, 1921.

15. Powers, G. F.: Unpublished data.

16. Streeter, G. L.: Weight, Sitting Height, Head Size, Foot Length, and Menstrual Age of the Human Embryo, Publication 274, Carnegie Institution of Washington, 1920; Contrib. Embryol. **2**:143, 1920.

fetus gains from 1,045 to 1,680 Gm. during the eighth lunar month, and according to Scammon and Calkins [17] from 988 to 1,537 Gm. These gains are at the rate of 16.6 and 15.5 Gm. per kilogram of mean body weight per day, respectively.

Although the number of infants fed human milk in this study was small, the data point in two ways to the inadequacy of human milk. First, the gains in weight on human milk for the whole group were less than on cow's milk (the figure). Second, the rate of gain in weight was less for smaller (11.7 Gm. per kilogram per day) than for larger

TABLE 4.—*Gains in Weight of Fourteen Premature Infants Whose Weights Were Less Than One Thousand Grams on Admission and Who Were Fed Mixtures of Partially Skimmed Cow's Milk.*

Name	Sex	Estimated Degree of Prematurity, Weeks	Birth Weight, Gm.	Minimum Weight		Age When Birth Weight Was Regained, Days	Age at 2,500 Gm., Days	Mean Weight Gain 7th-28th Day, Gm./Kg./Day
				Gm.	Age, Days			
Ho.*	F	15	662	580	6	11	85	18.4
Tr.	F	9	800 †	800	8	21	91	15.8
Sh.‡	F	..	810 ?	...	..	..	93	....
To.	F	12	872	794	6	13	104	12.0
Lap.	F	11	900 §	890	9	14	70	16.3
Fe.‖	M	10	900 ?	838	5	11	68	22.3
Hu.¶	M	..	908 ?	723	5	17	70	21.5
Cr.	F	9	930	785	8	18	86	14.7
Lan.	F	12	936	860	12	21	77	....
Lat.	M	0	956	956	1	1	70	19.9
McG.	F	5	980	888	6	12	69	15.9
Ri.	F	13	992	879	7	15	118	....
Or.	F	14	1,000	820	5	15	75	17.9
Ma.#	F	..	1,088 ?	894	5	12	63	20.4

* Ho. was a Negro.
† Tr. was not weighed until the eighth day.
‡ The initial weight of Sh. at the New York Hospital was 950 Gm. at 34 days.
§ Lap. was not weighed until the third day.
‖ The initial weight of Fe. at the New York Hospital was 834 Gm. at 5 days.
¶ The initial weight of Hu. at the New York Hospital was 723 Gm. at 4 days.
# The initial weight of Ma. at the New York Hospital was 952 Gm. at 36 hours.

infants (12.7 Gm. per kilogram per day) on human milk. An optimal foodstuff might be expected to promote a more rapid rate of gain in smaller infants. Such an inverse relation was found for the cow's milk feedings but not for the human milk.

Since there is no significant difference between the results for the larger infants on the three diets, it seems wise to feed the infants of this weight group their own mothers' milk when easily obtainable from

17. Scammon, R. E., and Calkins, L. A.: Growth in the Fetal Period, Minneapolis, Minn., University of Minnesota Press, 1929.

individual mothers in order to stimulate their milk supply and thus permit more infants to be discharged from the hospital on breast feedings. The desirability of such a procedure from a psychologic standpoint cannot be gainsaid for a situation already fraught with so much anxiety.[18] In Stockholm [19] mothers are permitted to nurse their infants in the nursery when the latter attain weights above 2,000 Gm. and are strong enough to go to breast. For infants too weak to be put directly to breast, the feeding of even human milk becomes, however, an artificial procedure. Properly modified mixtures of cow's milk are then more suitable, at least under conditions of hospital practice, where cleanliness, good refrigeration and intelligent supervision of the feeding are available.

Since clinical impression of the superiority of human milk is so widespread, it is important that other clinics housing adequate numbers of small premature infants undertake similar studies, comparing the rate of progress of infants fed isocaloric amounts of the feeding mixtures under the same medical, nursing and environmental conditions. Such studies are not now present in the literature.

SUMMARY

A group of 122 prematurely born white infants, whose weights at birth ranged from 1,022 to 1,996 Gm., were fed diets containing 120 calories per kilogram of either human milk, a simple mixture of evaporated cow's milk or a mixture of partially skimmed cow's milk under similar conditions of environment and medical and nursing care.

The mean gains in weight per kilogram per day for a period from the seventh to the twenty-eighth day were significantly larger for the two groups of infants fed cow's milk than for the group fed human milk. The infants fed the mixture of half-skimmed milk gained more rapidly than those fed evaporated milk.

When the infants were divided into two groups according to mean weight at birth, similar but even more striking differences were found to exist for the "smaller" infants. For the larger infants, the differences were insignificant.

Fourteen infants whose weights at admission were less than 1,000 Gm. gained well on the mixture of half-skimmed milk, the rate of gain approximating that of the "smaller" infants in the larger study.

18. Shirley, M.: A Behavior Syndrome Characterizing Prematurely Born Children, Child Development **10**:115, 1939. Koenig, H.: The Care of Premature Infants: A Plan of Cooperation Between Hospital and Public Health Nursing Services, Child **5**:65, 1940.

19. Lichtenstein, A.: Personal communication to the authors.

CONCLUSIONS

Under conditions of modern hospital practice, with cleanliness, good refrigeration and careful supervision of feeding, the use of mixtures of cow's milk in amounts designed to give approximately 120 calories per kilogram will produce larger gains in weight in premature infants than will human milk. Mixtures of partially skimmed cow's milk are particularly indicated for smaller premature infants.

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ERYTHEMA INFECTIOSUM

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ERYTHEMA infectiosum is an acute infectious disease found usually in children and characterized by an evanescent rose-red morbilliform eruption which spreads rapidly from the face to the extremities with no other symptoms. The literature indicates that the disease is not geographically limited. The recent increase in reports of small epidemics indicates that for years the disease probably has been confused with other exanthems. The possibility of exposing a young victim of this mild malady to virulent organisms in isolation wards is apparent. It is the purpose of this paper, therefore, to report a recent epidemic in Milwaukee and to indicate the paramount features of the disease according to our observations and a study of the literature.

Erythema infectiosum usually occurs in small epidemics and, although no careful statistical studies have been made, it appears that girls are more frequently afflicted. Though the cause is not definitely established [1] a virus is suspected. The disease usually runs its course in from six to ten days, although the duration may vary from three to twenty days. Palliative treatment is all that is indicated. There are no sequelae other than an occasional slight desquamation of the face.[1] The sedimentation rate shows no change. The white blood cell count is within normal limits. The incubation period has not been established,[2] but is probably about two weeks. The characteristic rash with an absence of other symptoms is diagnostic.

From February of 1944 until mid-July of the same year, 22 cases were observed in Milwaukee. The youngest patient was 4 years of age, and the oldest 24. Twelve were girls and 10 were boys. The highest case frequency was between 9 and 11 years. Though no 2 cases were precisely alike, they presented a clearcut clinical syndrome. Careful observation of 1 case assures correct diagnosis of subsequent cases. Our observations in general agree with those previously outlined by

From South View Isolation Hospital for the Milwaukee Health Department and the Department of Clinical Medicine, Marquette University School of Medicine.

1. Shaw, H. L. K.: Erythema Infectiosum, Am. J. M. Sc. **129**:16, 1905.

2. Hanneman, Y.: Over den incubatietijd van erythema infectiosum, Nederl. tijdschr. v. geneesk. **70**:1984 (Oct. 30, pt. 2) 1926.

other workers in this field, notably Schlossmann.[3] Uniformly the first symptom is a flushed face. The exanthem is most dense in the region of the glabella and under the eyes, the butterfly area, and creates an impression of circumoral pallor by being conspicuously absent from the upper lip, the nasolabial folds and frequently the chin. This is characteristic. Soon afterward, within a day or two, the exanthem usually fades from the face and becomes generalized over the entire body except for the palms and the soles, and often the chest, the abdomen, the back and the flexor surfaces of the extremities. There is nothing characteristic about this, and if the diagnostician is not careful he is apt to confuse it with other exanthems, especially measles. The process continues so that large blotches appear to be on a polkadot background, particularly on the extensor surfaces of the arms and the legs. We observed no incidence of pruritus or edema. The entire course is afebrile, though some workers mention a slight elevation of temperature, to 99 to 99.5 F. The exanthem has an evanescent character and changes in color with temperature or emotion or direct irritation such as rubbing.[4] Gradually the color fades, first from within the large blotches, leaving a characteristic lattice work appearance. With complete fading there is seldom desquamation. The entire course most frequently requires from six to ten days. We have never observed manifestations other than the rash, nor did we see an enanthem. Due to the usual unpredictable variations in adolescence, the leukocyte count cannot be relied on as an aid to diagnosis.

Since the rash is the most obvious sign of the disease, we insert here three photographs of a 6 year old patient who had no other objective symptoms, was afebrile and whose case lasted six days with no sequelae. This case is typical of those in our Milwaukee epidemic.

Erythema infectiosum has been most often confused with measles. Tschamer[5] in 1886 was the first to describe the disease, calling it "örtliche Rötheln." The rash puzzled him, for it differed somewhat from the usual rash of measles. He concluded that it was an atypical form of German measles. Gumplowicz[6] in 1891, though he agreed with this interpretation, showed that measles conferred no immunity against this newly noted exanthematous syndrome and vice versa.

Tobeitz[7] in reporting a number of similar cases confirmed earlier conclusions. He believed that specific alterations in the causal agent

3. Pfaundler, M., and Schlossmann, A.: The Diseases of Children, translated by M. G. Peterman, Philadelphia, J. B. Lippincott Company, 1935, vol. 3, p. 221.

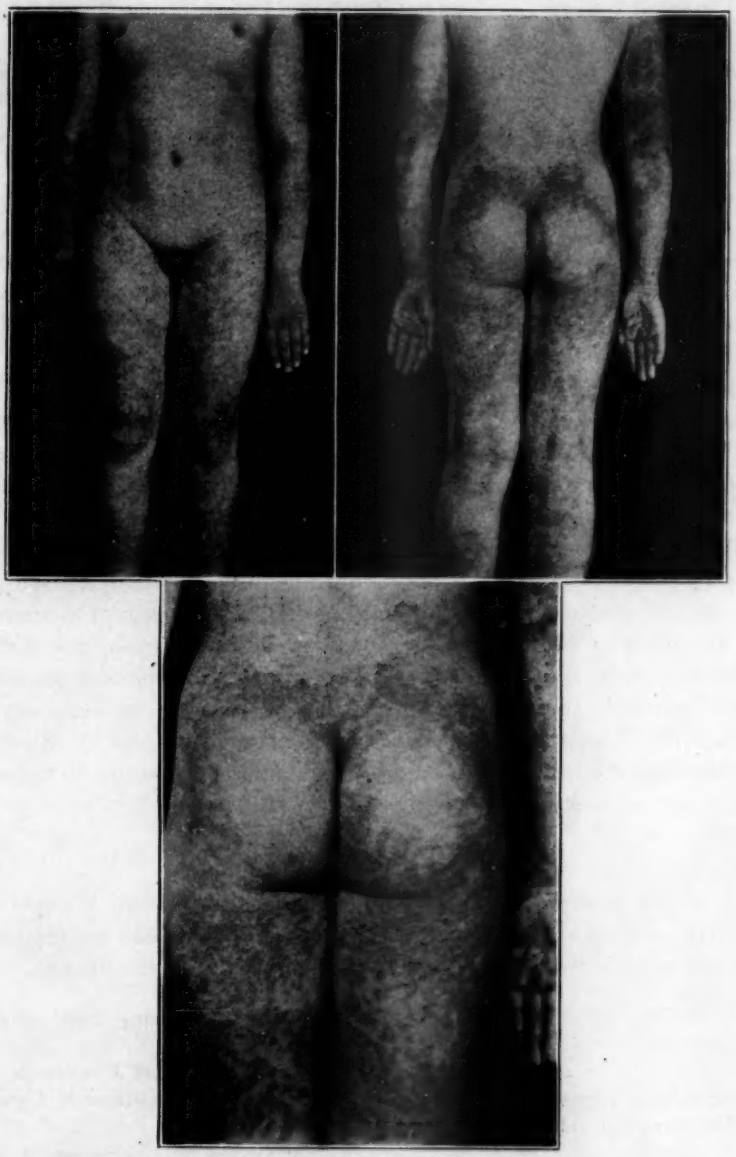
4. Monastra Abate, A.; Debenedetti, V., and Gallotti, E.: Su di una epidemia di 124 casi di quinta malattia, Pediatria **42**:374 (April) 1934.

5. Tschamer, A.: Ueber örtliche Rötheln, Jahrb. f. Kinderh. **29**:372, 1889.

6. Gumplowicz, L.: Casuistisches und historisches über Rötheln, Jahrb. f. Kinderh. **32**:266, 1891.

7. Tobeitz: Zur Polymorphie und differential Diagnose der Rubeola, Arch. f. Kinderh. **25**:17, 1898.

of German measles were responsible for the symptoms. His assistant, Escherich,[8] however, realized that when the cause is unknown the basis for the classification of an exanthematous disease is its clinical syndrome



Three photographs of a 6 year old patient with erythema infectiosum.

8. Escherich, T.: Variété d'erythème infectieux chez les enfants, Cong. internat. de méd., Compt.-rend., 1900, p. 528.

and not speculation concerning the cause. He declared, therefore, that this was a specific new disease entity, classified it and later reported two more epidemics at Graz.

The present name, "erythema infectiosum," was originated by Sticker[9] in 1899. Berberich,[10] a student of Sticker, described 45 cases.

A series of German reports followed describing similar "diseases" which Shaw, and later many of the authors themselves, recognized as erythema infectiosum.[1]

In 1905, Shaw [1] aroused American interest and investigation by his essay concerning a Viennese series. Subsequently, American epidemics were recorded by Zahorsky,[11] of the St. Louis Pediatric Society, in 1924; Herrick,[12] of Cleveland, in 1924 and 1925; Feeley [13] in 1928, and Lawton and Smith [14] in 1930. Colored drawings of the rash illustrate Shaw's paper, and photographs accompany those of Herrick and Lawton and Smith.

In recent years, epidemics of this disease have been reported in cities in all parts of the world. For the most part, they have been small and have occurred during the warmer months, usually reaching a peak in three or four weeks and then subsiding. These epidemics indicate the contagious nature of erythema infectiosum.

The disease is assumed to be spread by droplets, not by fomites or carriers, although the actual mode of transmission is not definitely known. The causative organism has not been demonstrated. In regard to immunity, an attack of the disease has not been shown to make the person resistant to later exposure. It has been shown that measles does not confer immunity to erythema infectiosum and that the opposite is not true either. The incidence is highest in the age group of 3 to 12 years. The fact that the incidence in adults and infants is low seems to indicate that some immunity is developed.

SUMMARY

A recent Milwaukee epidemic of erythema infectiosum is reported. The paramount features in the development of this disease are reported. The literature is reviewed to indicate the prevalence of the disease.

9. Sticker, G.: Die neue Kinderseuche in der Umgebung vom Giessen, Erythema infectiosum, Ztschr. f. prakt. Arzte. **40**:121, 1899.

10. Berberich, E.: Eine Epidemie von acutem Erythem bei Kindern in der Umgebung von Giessen (Erythema infectiosum acutum), Inaug. Dissert., Giessen, von Munchow'sche Druckerei, 1899.

11. Zahorsky, J.: Case of Erythroedema Complicated by Noma, Am. J. Dis. Child. **28**:261 (Aug.) 1924.

12. Herrick, T. P.: Erythema Infectiosum, Am. J. Dis. Child. **31**:486 (April) 1926.

13. Feeley, J. B.: Erythema Infectiosum, Atlantic M. J. **31**:752 (July) 1928.

14. Lawton, A. L., and Smith, R. E.: Erythema infectiosum: Clinical Study of an Epidemic in Branford, Conn., Arch. Int. Med. **47**:28 (Jan.) 1931.

CONCLUSIONS

1. Erythema infectiosum should be considered in the diagnosis of any exanthem of children appearing during the summer months.

2. An evanescent rose-red morbilliform eruption, spreading rapidly from the face to the extremities with an absence of other signs and symptoms, is diagnostic.

3. Patients with this mild disease should not be exposed to the virulent organisms prevailing in isolation wards.

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JUVENILE OSTEOPETROSIS

Metabolic Studies in Two Cases and Further Observations on the Composition of the Bones in This Disease

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REPORTS of cases of osteopetrosis have hitherto dealt mostly with the clinical and pathologic aspects of this disease. Studies of the mineral balance and chemical analyses of the bones have been few in number. Laurell and Wallgren [1] were first to study the calcium balance in a 12 year old child suffering from osteopetrosis. They found positive calcium balances in all periods studied and "no tendency towards an abnormally high retention of calcium." Flood [2] found a positive calcium balance and a normal partition of this element between the urine and the stools in his case (the patient was a 12 year old girl). An outstanding observation in his case was of the presence of hypercalcemia. Bernhardt [3] found in a 26 year old man a slightly negative calcium balance which became positive on the addition of tertiary calcium phosphate to the diet. The composition of the diet (with respect to calcium and phosphorus) is not given. When ammonium chloride was administered to this patient hypercalcemia developed (14.5 mg. of calcium per hundred cubic centimeters). Clifton [4] obtained positive calcium balances in a 5½ year old child under all the conditions of his experiments, i. e., during the preliminary period and when ammonium chloride, thyroid, anterior pituitary and solution of parathyroid were administered. During the preliminary period the calcium was equally distributed between the urine and stool. When ammonium chloride was administered there was a pronounced excretion of calcium in the urine. Thyroid was ineffective in influencing the partition of calcium. Thyro-

From the Pediatric Department of the Jewish Hospital of Brooklyn.

1. Laurell, H., and Wallgren, A.: Untersuchungen über einen Fall einer eingenartigen Skeletterkrankung (Osteosclerosis fragilis generalisata), Upsala läkaref. förh. **25**:309 (Nov. 8) 1920.

2. Flood, R. G.: Calcium Metabolism in Marble Bones (Albers-Schönberg Disease): Report of a Case, California & West. Med. **31**:203 (Sept.) 1929.

3. Bernhardt, H.: Ein Beitrag zur Marmorknochenerkrankung (Albers-Schönbergsche Krankheit), Klin. Wchnschr. **5**:415 (March 5) 1926.

4. Clifton, W., and others: Osteopetrosis (Marble Bones), Am. J. Dis. Child. **56**:1020 (Nov.) 1938.

tropic substance was also without effect. The administration of parathyroid produced no demonstrable effect. The concentration of calcium and phosphorus in the patient's serum was not influenced by the administration of any of these substances. In the exhaustive report by McCune and Bradley [5] on marble bones a study of both calcium and phosphorus balances is included. These authors stated that because of the coexistence of healing rickets in the patient during the period of their studies the results of their experiment cannot be clearly interpreted.

We have had the opportunity of studying 2 infants suffering with osteopetrosis. A complete clinical and pathologic report of 1 of our cases has already been published.[6]

Fig. 1.—Roentgenogram showing features characteristic of osteopetrosis and also of rickets.

REPORT OF CASES

CASE 1.—R. H., a boy 3½ months old, showed considerable undernutrition, pallor, bossing of the frontal and parietal bones, swelling of the epiphyses of the long bones, a large liver and spleen and optic atrophy. He had severe anemia and evidence of erythromyelopoiesis. The concentration of calcium in the serum was 8.8 mg. per hundred cubic centimeters, the concentration of inorganic phosphorus was 3.1 mg. and the value for phosphatase was 23 units (Bodansky).

5. McCune, D. J., and Bradley, C.: Osteopetrosis (Marble Bones) in an Infant: Review of Literature and Report of a Case, Am. J. Dis. Child. **48**:949 (Nov.) 1934.

6. Kramer, B., and Halpert, B.: Marble Bones: Clinicopathological Observations, Am. J. Dis. Child. **57**:795 (April) 1939.

Roentgenograms of the long bones showed features characteristic of osteopetrosis and also of healing rickets (fig. 1). The period of observation of this child was short. The child remained at the hospital for about one month, and we were able to study his mineral balance for only one period.

CASE 2.—E. A., a girl, was 10 weeks old when first seen. In this instance consanguinity was present (the father and the mother were first cousins). Her nutrition was fair, but she had a noticeable pallor. The liver and the spleen were enlarged. Considerable optic atrophy was found. Erythromyelopoiesis was also present. The concentration of calcium in the serum was 8.5 mg. per hundred cubic centimeters, and of inorganic phosphorus 2.4 mg.; there were 20.8 units (Bodansky) of phosphatase activity. Roentgenograms of the long bones revealed evidence of osteopetrosis but failed to show changes in the epiphyses of either

Fig. 2.—Roentgenogram showing evidence of osteopetrosis but not showing changes indicative either of active or of healing rickets.

active or healing rickets (fig. 2). The patient remained under observation for sixteen months. The child died from uncontrolled hemorrhage. The abnormalities noted at necropsy were those which are characteristic of osteopetrosis, namely, hypoplasia of the bone marrow and hemopoiesis in the spleen, the liver, the lymph nodes, the kidneys and the lungs. Splenomegaly and hepatomegaly were striking. The thyroid, the parathyroid and the pancreas appeared to be normal grossly and microscopically. The hypophysis was not examined. The adrenal glands showed a moderate degree of hypoplasia.

Studies of the mineral balances included determinations of calcium, phosphorus, sodium, potassium, magnesium, chlorides and nitrogen. We made observations on the concentrations in the serum of total lipids, lipid phosphates, cholesterol and its esters. The stools of both patients were analyzed for total fat, fatty acids and soaps. The Hamilton and

Schwartz[7] test for the presence of increased amounts of parathyroid hormone in the blood was done on several occasions. The concentrations of calcium, phosphorus and phosphatase in the blood serum were determined at intervals during the studies.

Since the parathyroid glands are held by some observers to be in some manner linked with the production of this syndrome, we studied the effect of the administration of parathyroid on the calcium, the phosphorus and the phosphatase in the blood serum. This study lasted about two months. During the first eleven days of our study 30 units of parathyroid was administered daily, while during the subsequent forty-six days 60 units was administered every day.

Our metabolic studies were done for three day periods with the exception of two experiments, one on R. H. and the other on E. A., which were continued for six days but were calculated as for three day periods. Preliminary studies of metabolic balance were done in both instances. In the case of R. H. this was the only study possible, but in the case of E. A. subsequent studies followed the administration of vitamin D_2 derived from ergosterol and dissolved in propylene glycol (Drisdol). R. H. received evaporated milk and water (equal parts) with 5 per cent solution of Dextri-Maltose, while E. A. received a mixture of 15 ounces (425.2 Gm.) of whole milk plus 5 ounces (141.7 Gm.) of water with 5 per cent solution of Dextri-Maltose no. 1. The diet of R. H. yielded 96 calories per kilogram per day and had a calcium-phosphorus ratio of 1.2, and that of E. A. yielded 68, 80, 93, 109 calories per kilogram per day for the first, second, third and fourth periods, respectively. The calcium-phosphorus ratio in the diet throughout all periods was 1.3. Samples of the diet were analyzed for calcium, phosphorus, potassium, sodium, magnesium, chlorides and nitrogen. The daily intake was measured accurately, and the urine and stools were collected each day. In the collection of feces the beginning and the end of each period were marked off by oral administration of carmine. At the beginning of each metabolic study the blood serum was analyzed for calcium, inorganic phosphorus and phosphatase. Following the control period, 60 drops of vitamin D_2 was added daily to the diet of E. A. This was continued for several weeks, and another balance study was made. We noted a rise in the concentration in the blood serum of calcium and inorganic phosphorus and a lowering of the phosphatase level (table 1). We therefore decided to continue the administration of vitamin D. Four days later another balance study was done. At the end of this period the concentration in the blood serum of calcium and

7. Hamilton, B., and Schwartz, C.: A Method for Determination of Small Amounts of Parathyroid Hormones, J. Pharmacol. & Exper. Therap. **46**:285 (Nov.) 1932; Rickets and Hyperparathyroidism, Am. J. Dis. Child. **46**:775 (Oct.) 1933.

inorganic phosphorus indicated a more advanced healing of the rachitic process. We therefore thought it advisable to allow a longer time to elapse before doing more studies of the mineral balance. Five months later the last study was made. During this interval vitamin D was continuously given.

TABLE 1.—*Chemical Composition of the Blood of Patient E. A. During the Entire Period of Study*

Date	2/7	2/21	3/10	3/24	4/28	5/23	6/16	6/23	7/25	9/15	10/19
Calcium *	8.5	7.8	7.6	8.7	9.4	9.5	8.3	8.5	9.4	8.7	9.9
Phosphorus *	2.4	1.5	3.6	3.7	4.6	5.0	4.6	...	5.6	5.5	5.5
Potassium *	19.6	...	...	...	...	...	7.4	...	...	...	...
Chlorine *	378	...	...	...	...	...	...	353	...	...	...
Magnesium *	2.4	...	...	...	...	...	...	...	...	...	...
Total lipids *	508	...	...	...	...	...	...	...	...	...	...
Lipid phosphorus *	4.8	...	...	...	...	...	...	...	...	...	...
Total cholesterol *	125	...	...	...	164	...	...	148	145	119	...
Free cholesterol †	34	...	...	...	...	...	...	...	...	...	...
Nonprotein nitrogen *	23	...	...	...	...	...	...	24.4	25.2	28.6	...
Urea *	8.6	...	...	...	...	...	...	...	...	...	...
Sugar *	63	...	...	...	...	...	90	...	93	...	...
Albumin †	2.73	...	...	...	...	...	...	3.68	4.09	...	...
Globulin †	2.47	...	...	...	...	...	...	2.66	1.96	...	...
Fibrinogen †	0.176	...	...	...	...	...	...	...	...	...	...
Phosphatase ‡	20.8	9.5	13.2	11	...	4.9	7.4	...	10	3.7	3.7

* Milligrams per hundred cubic centimeters.
† Grams per hundred cubic centimeters.
‡ Bodansky units.

RESULTS

The metabolic studies revealed, in the case of R. H. (table 2), a positive balance for all the mineral elements studied. The retention ratio for calcium and phosphorus was 1.9, as is seen in healing rickets. This observation was further corroborated by the increased deposition of

TABLE 2.—*Mineral Metabolism in Osteopetrosis (Patient R. H.)*

	Calcium *	Phosphorus *	Sodium *	Potassium *	Magnesium *	Chlorine *	Nitrogen *	Comment
Urine	0.002	0.739	0.431	1.925	0.000	1.215	4.319	Weight 4,370 Gm.; age
Stool	0.718	0.182	0.000	0.099	0.089	0.000	0.833	3½ mo.; period 10/2/35 to
Total	0.720	0.921	0.431	2.024	0.089	1.215	5.152	10/8/35; 3 day balance;
Intake	1.782	1.481	1.435	2.485	0.375	2.742	8.250	blood: Ca 8.8, 8.2, 7.8
Balance	1.062	0.560	1.004	0.461	0.286	1.527	3.098	mg.; P 3.1, 3.1 2.6 mg.;
Balance, Gm./Kg./day	0.060	0.042	0.076	0.033	0.022	0.116	0.234	phosphatase 23 u., 28.5 u.

* Grams.

calcium salts in the metaphyses (fig. 3). The product of the calcium and the phosphorus in the serum, however, remained in the so-called rachitic zone, and the level of phosphatase in the serum remained high. The urinary and fecal partition of phosphorus was that ordinarily found in healing rickets; i. e., about 70 per cent of the total phosphorus excreted appeared in the urine.

In the case of E. A. the preliminary period showed a positive balance for all minerals studied (table 3). The amount of calcium and phosphorus retained per kilogram per day was much lower than in the case of R. H. The retention ratio of calcium to phosphorus was 2.6 instead of 1.9, as was found for R. H. The product of the calcium and the phosphorus in the serum was that which obtains in active rickets.

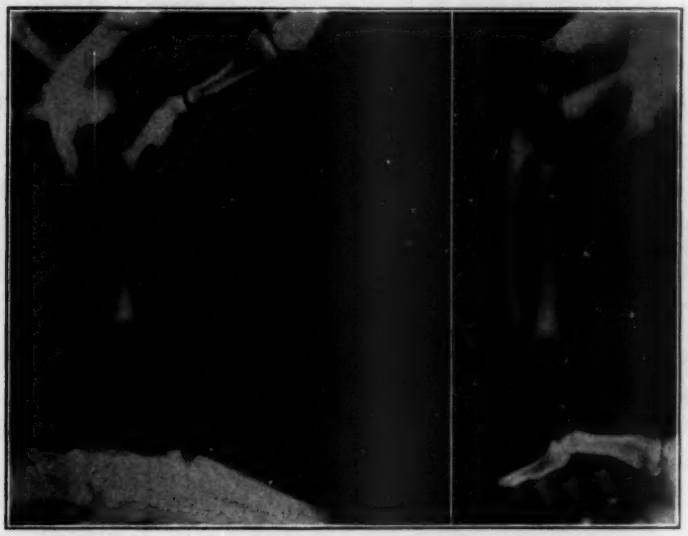

Fig. 3.—Roentgenogram showing increased deposition of calcium salts in the metaphyses.

TABLE 3.—*Mineral Metabolism in Osteopetrosis, Preliminary Period (Patient E. A.)*

	Calcium *	Phosphorus *	Sodium *	Potassium *	Magnesium *	Chlorine *	Nitrogen *	Comment
Urine.....	0.005	0.388	0.142	0.929	0.028	0.600	2.025	Weight 4,000 Gm.; age
Stool.....	0.270	0.123	0.025	0.191	0.136	0.000	0.328	2½ mo.; period 2/8/38 to
Total.....	0.275	0.511	0.167	1.120	0.164	0.600	2.953	2/11/38; blood (2/7/38):
Intake.....	1.137	0.850	0.965	1.646	0.252	1.699	4.540	Ca 8.5 mg., P 2.4 mg.,
Balance.....+0.862		+0.339	0.798	0.526	0.088	1.099	1.587	phosphatase 20.8 u.
Balance, Gm./ Kg./day.....+0.065		+0.025	0.058	0.038	0.006	0.080	0.115	

* Grams.

The phosphatase level was high. (The urinary excretion of phosphorus was, however, that usually found in healing rickets, i. e., about 76 per cent of the total excretion was eliminated in the urine.) The roentgenograms showed no evidence of rickets (fig. 2). The period of study which followed the administration of vitamin D_2 for seven weeks showed an increase of 20 per cent in the retention of phosphorus (table 4). All minerals studied with the exception of sodium chloride gave a positive

balance. A negative balance of sodium chloride may be found in the early stages of healing rickets.[8] The phosphatase activity dropped from 20.8 to 11 units and the inorganic phosphorus rose from 2.4 to 3.7 mg. per hundred cubic centimeters. The retention of calcium per kilogram per day showed an increase from the original 65 mg. to 72 mg., and the phosphorus increased from 25 mg. to 43 mg. (tables 4 and 5). In all sub-

TABLE 4.—*Mineral Metabolism in Osteopetrosis After Administration of Sixty Drops of Vitamin D_2 a Day from Feb. 12, 1938 (Patient E. A.)*

	Calcium *	Phosphorus *	Sodium *	Potassium *	Magnesium *	Chlorine *	Nitrogen *	Comment
Urine.....	0.002	0.394	0.998	1.054	0.032	1.964	3.629	Weight 4,300 Gm.; age 4½ mo.; period 4/5/38 to 4/11/38; 3 day balance; blood (3/28/38): Ca 8.7 mg.; P 3.7 mg.; phosphatase 11 u.
Stool.....	0.356	0.116	0.159	0.488	0.183	0.000	0.316	
Total.....	0.358	0.510	1.157	1.542	0.215	1.964	3.945	
Intake.....	1.200	0.894	1.016	1.736	0.266	1.787	4.788	
Balance.....	0.842	0.384	—0.141	0.194	0.051	—0.177	0.843	
Balance, Gm./Kg./day.....	0.065	0.030	—0.011	0.013	0.004	—0.014	0.065	

* Grams.

sequent experiments the sodium and chloride showed a positive balance. The concentration of calcium in the blood serum increased from 8.5 to 9.4 mg. per hundred cubic centimeters, and the concentration of inorganic phosphorus increased from 2.4 to 4.6 mg. Five months later we found

TABLE 5.—*Mineral Metabolism in Osteopetrosis with Continued Administration of Vitamin D_2 (Patient E. A.)*

	Calcium *	Phosphorus *	Sodium *	Potassium *	Magnesium *	Chlorine *	Nitrogen *	Comment
Urine.....	0.004	0.342	0.762	1.179	0.032	2.067	3.936	Weight 4,300 Gm.; age 5 mo.; period 4/15/38 to 4/18/38; blood (4/28/38): Ca 9.4 mg.; P 4.6 mg.
Stool.....	0.535	0.196	0.004	0.274	0.188	0.000	0.581	
Total.....	0.539	0.538	0.766	1.453	0.220	2.067	4.517	
Intake.....	1.471	1.099	1.246	2.130	0.326	2.198	5.873	
Balance.....	0.932	0.561	0.480	0.677	0.106	0.131	1.356	
Balance, Gm./Kg./day.....	0.072	0.043	0.037	0.052	0.008	0.010	0.105	

* Grams.

a retention of 91 mg. of calcium per kilogram per day and of 48 mg. of phosphorus (i. e.; 40 per cent more of the calcium and 92 per cent more of the phosphorus were retained than we found in our preliminary experiment) (table 6). A positive balance was obtained for all the other minerals studied. At this time the concentration of calcium

8. Heymann, W.: Nitrogen, Potassium, Sodium and Chloride Metabolism in Rickets, with Special Reference to Biliary Fistula Rickets in Puppies, J. Exper. Med. **64**:471 (Sept.) 1936. Gittleman, I. F., and Pincus, J. B.: Rickets Associated with Dwarfism, Glycosuria, Ketonuria and Albuminuria, Am. J. Dis. Child. **60**:1351 (Dec.) 1940.

in the serum was 8.7 mg. per hundred cubic centimeters and of phosphorus was 5.5 mg. The phosphatase activity in the serum was 3.7 units. The product was definitely within the healing zone. The roentgenograms taken at various intervals showed a progressive healing of

TABLE 6.—*Mineral Metabolism in Osteopetrosis with Continued Administration of Vitamin D_2 (Patient E. A.)*

	Calcium *	Phosphorus *	Sodium *	Potassium *	Magnesium *	Chlorine *	Nitrogen *	Comment
Urine.....	0.013	0.752	1.136	2.311	0.139	2.482	8.081	Weight 6,200 Gm.; age
Stool.....	0.787	0.218	0.000	0.130	0.234	0.000	0.543	10 mo.; period 9/19/38 to
Total.....	0.801	0.970	1.136	2.441	0.373	2.482	8.574	9/22/38; blood (9/15/38);
Intake.....	2.492	1.862	2.112	3.606	0.553	3.725	4.952	Ca 8.7 mg.; P 5.5 mg.;
Balance.....	1.691	0.892	0.976	1.167	0.180	1.243	1.378	phosphatase 3.7 u.
Balance, Gm./Kg./day.....	0.091	0.048	0.054	0.063	0.010	0.066	0.074	

* Grams.

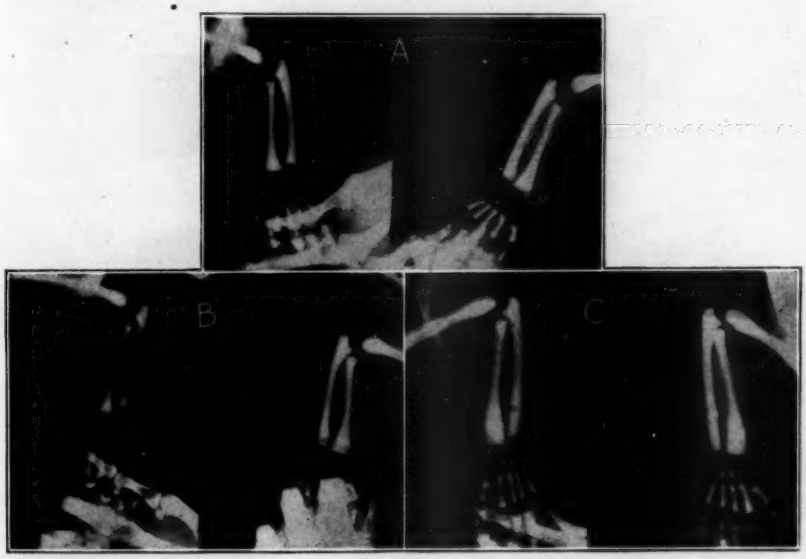

Fig. 4.—Roentgenograms showing a progressive healing of the rachitic process. *A*, roentgenogram taken March 3, 1938. *B*, roentgenogram taken April 25. *C*, roentgenogram taken May 11.

the rachitic process (fig. 4). The urinary excretion of phosphorus, however, remained constantly at the level of about 75 to 80 per cent of that of the total. A diagrammatic representation of our observations may be seen in figure 5.

The effect of parthyroid on 1 of our patients, E. A., was studied over a period of two months. Weekly determinations of the calcium, the phosphorus and the phosphatase in the serum were done. For the

first eleven days, 30 units of parathyroid and 10 drops of vitamin D_2 were given daily. The dose of parathyroid was increased to 60 units for the following forty-six days. We noted a gradual rise in the concentration of calcium in the serum and a gradual drop in the concentration of phosphorus. The calcium, however, did not rise above the so-called level for normal infants of her age. The phosphorus level

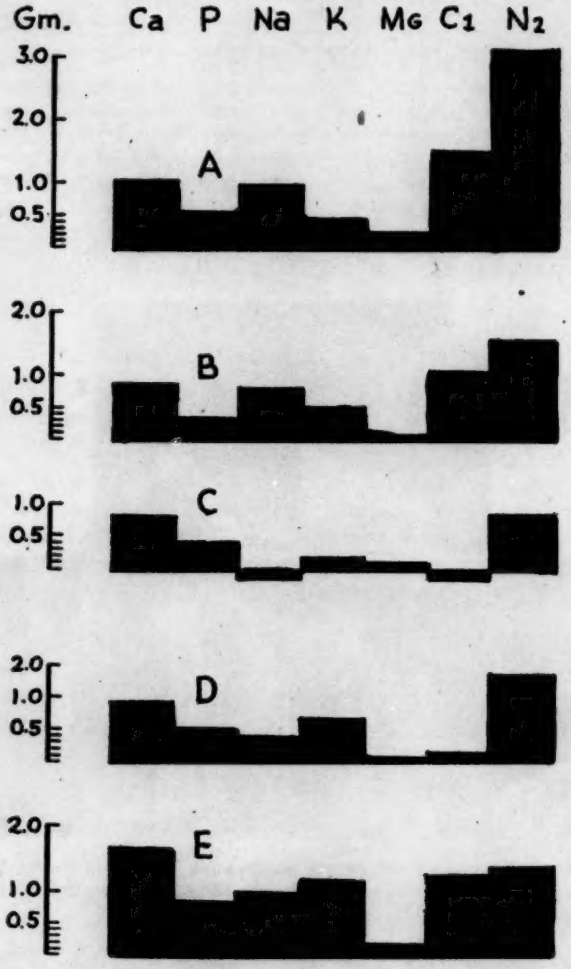

Fig. 5.—Metabolic studies on patients R. H. and E. A. *A*, study on patient R. H. at age of 3½ months. The study was continued for six days (Oct. 2 to Oct. 8, 1935) but has been calculated as for a three day period. Vitamin D_2 had not been given. *B*, study on E. A. at age of 2½ months, Feb. 8 to Feb. 11, 1938. Vitamin D had not been given. *C*, study on E. A. at age of 4½ months. The study was continued for six days (April 5 to April 11) but was calculated as for a three day period. Vitamin D_2 had been given, 60 drops a day for seven weeks. *D*, study on E. A. at age of 5 months. Vitamin D_2 had been given, 50 to 60 drops a day for two months. *E*, study on E. A. at age of 10 months. Administration of vitamin D_2 had been continued.

gradually dropped from 5.5 mg. per hundred cubic centimeters of serum to 3 mg. The phosphatase was uninfluenced. After the level of calcium had reached 10.2 mg. and the level of phosphorus 3 mg. (this was obtained after a period of six weeks of administration of parathyroid) further administration of parathyroid failed to influence the calcium and phosphorus levels in the blood serum. In fact, it seemed that parathyroid lost all effect. The concentrations of calcium and of inorganic phosphorus in the patient's serum returned to a level held before the administration of parathyroid. After a month during which parathyroid was not administered, the concentration of calcium and of inorganic phosphorus in the serum remained at the level held at the beginning of the experiment. These results seem to bear out the observations of Pugsley and Selye [9] and others,[10] that the effect of parathyroid is not of a continuous or a progressive nature. Pugsley and Selye pointed out "that if parathyroid hormone was given to animals or man over a long period of time it lost its power to mobilize calcium, and in the later stages of the treatment the serum calcium might actually be reduced by the hormone instead of being increased." Selye explains this phenomenon as being due to the altered effect of the hormone from stimulating the formation of osteoclasts to that of bringing about the proliferation of osteoblasts. The hypercalcemia or the hypocalcemia therefore merely reflects the effect of parathyroid during the first or destructive stage or the later or proliferative stage, respectively.

COMPOSITION OF BONE TISSUE

In a previous article, Kramer, Yuska and Steiner [11] reviewed the available data on the quantitative chemical composition of the bones in cases of marble bones (osteopetrosis), compared the results with similar analyses of the bones of a presumably normal fetus, two normal newly born infants, a 10 year old child and a 29 year old adult and discussed the significance of their observations. They summarized their results as follows:

The percentage of ash, of calcium and of phosphorus in the bones of an infant with osteopetrosis, where the characteristic lesion was present, was distinctly

9. (*a*) Pugsley, L. I., and Selye, H.: The Histological Changes in the Bone Responsible for the Action of Parathyroid Hormone on the Calcium Metabolism of the Rat, J. Physiol. **79**:113 (July 28) 1933. (*b*) Pehu, M.; Policard, A., and Dufourt, A.: L'ostéopétrose au maladie des au marmoréens, Presse méd. **39**:999 (July 4) 1931. (*c*) Selye, H.: On the Stimulation of New Bone Formation with Parathyroid Extract and Irradiated Ergosterol, Endocrinology **16**:547 (Sept.-Oct.) 1932.

10. Telfer, S. V.: Studies in Calcium and Phosphorus Metabolism: Infantile Rickets; Excretion and Absorption of Mineral Elements and Influence of Fats in Diet on Mineral Absorption, Quart. J. Med. **20**:7 (Oct. 26) 1926.

11. Kramer, B.; Yuska, H., and Steiner, M.: Marble Bones: II. Chemical Analysis of Bone, Am. J. Dis. Child. **57**:1044 (May) 1939.

higher than in the corresponding bones of a normal newly born infant, except in the flat bones of the skull.

The ratio of residual calcium to phosphorus was in harmony with the idea that the calcium-phosphorus compound in marble bones is tertiary calcium phosphate.

In analyses of the upper and lower tibial epiphyses, evidence of a calcium-phosphorus compound having a lower ratio of calcium to phosphorus was obtained.

When calculated in terms of acid-base equivalents, the total fixed base content as determined by electrodialysis exceeded the sum of the calcium and the magnesium content by 1.2 to 5.9 per cent. Part of this excess of base undoubtedly was represented by the sodium and potassium content of the bone. There is therefore no major basic component in marble bones which is not represented by the well known elements calcium, magnesium, sodium and potassium.

The value of *n*, i. e., the molecular ratio of calcium phosphate to calcium carbonate in the bones of the infant with osteopetrosis, was found to be approximately 2, corresponding to that found in normal adult bone or in the bones of rachitic infants, i. e., has more carbonate than bones of normal infants of the same age.

There was a satisfactory agreement between the ash content as determined by heating dried fat-free bone at 500 C. and the ash content calculated on the assumption that calcium and magnesium exist as carbonates and that phosphorus is present as tertiary calcium phosphate. On the same assumption, determinations of the acid-base balance showed a slightly positive base balance.

The significant findings therefore are a high carbonate content and hypermineralization. A high carbonate content is also present in adult and rachitic bone and may account for the increased fragility. Hypermineralization is a finding inconsistent with the diagnosis of rickets. It is therefore likely that the combination of high carbonate content and hypermineralization characterizes the mineral content of marble bones.

The death of the child whose mineral metabolism is reported in this paper provided an opportunity to analyze the bones of a second patient with osteopetrosis. The patient was under treatment a long time, so that the rachitic condition was completely healed at the time of death. Intensive antiscorbutic therapy was also given so that we were reasonably certain that the lesion in the bones was that of uncomplicated osteopetrosis (table 7).

The ash content of the dehydrated fat-free bone varied between 67 and 72 per cent, while the values previously reported for normal subjects, including the 16 to 18 week fetus, a 5½ hour old infant, a 6 day old infant, a child 10 years old and an adult 29 years of age, varied from 64.5 in the fetus to 61.5 in the 10 year old child. The ash content, calculated on the assumption that the mineral matter is made up of tertiary calcium phosphate, calcium carbonate and magnesium phosphate, agreed with the actual ash content within the limits of error of the method. The ratio of organic matter to ash was 0.494, 0.39 and 0.40. In presumably normal bones the ratio varied between 0.55 and 0.81, indicating a larger amount of ash per unit mass of organic matter

in the bones of the patient with osteopetrosis. The residual calcium-phosphorus ratio indicates that the chief compound has the stoichiometric proportions of tertiary calcium phosphate, while the lower values of n indicate a higher proportion of calcium carbonate. The chemical picture, therefore, which characterizes marble bones is one showing a high ash content per unit mass of dry fat-free bone, a lower ratio of organic matter

TABLE 7.—*Experimental Data in Case of Osteopetrosis (Patient E. A.)*

	Rib			Lumbar	
	Shaft	Knob	Bone and Cartilage	Vertebra	Top of Femur
Water content (by drying at 110 C.)	20.4%	19.5%	14.7%	33.4%	24.2%
Fat content (of dried bone)	7.00	5.98	6.40	2.91	1.75
Inorganic constituents (based on dry, fat-free bone)					
Calcium	25.80	26.35	26.76	27.13	27.16
Phosphorus	12.07	12.28	12.47	12.64	12.68
Magnesium	0.54	0.54	0.55	0.50	0.54
CO_2	3.57	4.03	4.05	4.15	4.00
Ash	67.06	72.04	71.33	71.92	72.05
Calculations, calcium and phosphorus relationships					
I. Assuming that all CO_2 is bound to calcium					
(a) Calcium combined with CO_2	3.24	3.66	3.68	3.77	3.64
(b) Residual calcium	22.56	22.69	23.08	23.36	23.52
(c) Phosphorus required for combination with residual calcium	11.61	11.71	11.91	12.02	12.11
(d) Magnesium assumed to be combined with PO_4 (since all CO_2 is combined with Ca); phosphorus combined with Mg	0.46	0.46	0.47	0.43	0.46
(e) Residual phosphorus	11.61	11.82	12.00	12.21	12.22
(f) $\frac{\text{Residual Ca}}{\text{Residual P}}$ (by weight) =	1.94	1.92	1.93	1.91	1.92
II. Assuming that all Mg is bound as $MgCO_3$					
(a) CO_2 required for Mg	0.98	0.98	1.00	0.91	0.96
(b) CO_2 left for combination with Ca	2.59	3.05	3.05	3.24	3.02
(c) Ca combined with CO_2	2.36	2.77	2.77	2.94	2.74
(d) Residual Ca	23.44	23.58	23.99	24.19	24.42
(e) $\frac{\text{Residual Ca}}{\text{P}}$ (by weight)	1.95	1.92	1.93	1.91	1.93
III. $n Ca_3(PO_4)_2.CaCO_3$ $n = \frac{\text{1/3 residual Ca}}{\text{Ca combined with } CO_2}$	2.31	2.07	2.09	2.06	2.15
IV. Actual ash	67.06	72.04	71.33	71.92	72.05
Calculated ash	68.16	70.00	71.03	72.01	71.99
Undetermined (probably Na + K)	−1.10	2.04	0.30	−0.09	0.06
Organic matter	32.94	27.96	28.67	28.08	27.95

to inorganic and a lower ratio of tertiary calcium phosphate to calcium carbonate. While undoubtedly the major portion of the organic matter consists of osteoid tissue a possible admixture with other material in the bone marrow cannot be excluded. Since the marrow spaces in osteopetrosis are small, this error would be less in the analyses of marble bones than in the analyses of normal bones. This may account in part for the higher ratio of organic matter to ash in normal bones.

When rickets complicated by osteopetrosis heals under the influence of vitamin D the architecture of the new bone as seen in the roentgenograms more closely resembles that of marble bones than that of normal bone.

COMMENT

In discussing the causation of osteopetrosis we have to consider the views held by two opposing schools of thought. One group of investigators [5] expressed the opinion that osteopetrosis is simply a developmental anomaly. They placed this disease in the class of developmental anomalies to which osteodystrophy or fragilitas ossium belongs. This contention is based on the following facts: (1) that this disease is familial; (2) that consanguinity is frequently associated with it; (3) that this disturbance seems to be a mixture of two mendelian characteristics, (*a*) a benign type which is a recessive and (*b*) a malignant form which is a mendelian dominant and (4) that no definite metabolic disturbance has been demonstrated to exist in this disease. These authors stated their belief that the developmental anomaly resides in the primordial mesenchymal cell which gives rise to the development of the elements of both bone and blood. Other observers [9] contended that osteopetrosis is due to a metabolic derangement caused by a hyperfunction of the parathyroid glands. The evidence on which they based this view is mainly indirect: (1) experimental production of osteopetrosis in animals by the injection of parathyroid over a long period of time [9c]; (2) the finding of a parathyroid tumor in 1 case of osteopetrosis,[9b] and (3) chemical data which report hypercalcemia in cases of osteopetrosis.[2]

Up to the present only one well controlled mineral metabolic study of both calcium and phosphorus was done on a child suffering from marble bones.[5] This study fails to throw any light on the presence or absence of a metabolic disorder in this disease because of the coexistence of healing rickets. We found that rickets seems to be regularly associated with juvenile osteopetrosis. In fact, it may be said that congenital rickets exists in this disease. One of our patients, E. A., when admitted to the hospital at the age of 10 weeks showed chemical evidence of florid rickets. It was therefore essential for us to attempt to dissociate the metabolic disturbance incident to rickets from an inherent metabolic disturbance characteristic of marble bones. We had the opportunity to do this when we compared the metabolic findings for one of our patients in whom osteopetrosis coexisted with healing rickets with those for another patient in whom osteopetrosis was associated with florid rickets. In the first instance our observations were identical with those of McCune and Bradley; i. e., 70 to 80 per cent of the total phosphorus excreted was found in the urine. This characterizes rickets in the healing state. However, when we studied our second patient, in

whom the rickets was in an active stage, we found a similar condition to exist; namely, 80 per cent of the phosphorus excreted was also lost by way of the urinary tract. The latter observation has never been made in uncomplicated active rickets. There is here, therefore, a disturbance other than that associated with the presence of rickets. We found that the partition of phosphorus remained unchanged throughout the period of observation (fifteen months) and was not influenced in any way by the administration or the witholding of vitamin D. It is also of interest in this connection to point out that the rickets in our patients was extremely resistant to vitamin D therapy. It took five months and the administration of large amounts of vitamin D to bring about a concentration of calcium and phosphorus in the blood which may be considered "normal" for the patient's age.

In order to make certain that the high level of excretion of phosphorus by way of the urinary tract is not due to a faulty absorption of calcium and phosphorus by way of the gastrointestinal tract, as is found in diarrheal disease,[10] we have analyzed the lipid partition of the stool for our patients and found that the total fat and the relationship between fat, neutral fat, fatty acids and soaps are normal. Besides, at no time did our patients have diarrhea during the periods of study. Since it is known that in hyperparathyroidism excretion of phosphorus by way of the urinary tract is greatly increased, we attempted to find whether abnormal amounts of parathyroid hormone existed in the patient's blood. The Hamilton and Schwartz test was done and found to elicit a negative reaction on two occasions.[12] However, these results do not rule out the presence of hyperparathyroidism.

The results of our metabolic studies and our serologic observations may readily be explained if we assume that hyperparathyroidism plays a role in the production of osteopetrosis. Our most important finding was the excretion of about 80 per cent of the total phosphorus in the urine. No other explanation for this peculiar fact except the probable existence of hyperparathyroidism is available to us at the present time. The persistent hypophosphatemia is also a cardinal characteristic of hyperparathyroidism. The absence of hypercalcemia, on the other hand, need not be considered as evidence against the presence of hyperparathyroidism.

We may add that our patients readily absorbed vitamin D from the intestinal tract. This would tend to disprove a contention held by some that this congenital malformation somehow is associated with a poor absorption of vitamin D.

12. The value of this test for the diagnosis of hyperparathyroidism has been questioned.

CONCLUSION

On the basis of the results obtained in our metabolic studies we may conclude that while a congenital malformation of the primordial mesenchymal cell may exist we are certainly confronted by an associated metabolic disturbance which in its manifestations resembles a chronic state of hyperparathyroidism. Whether this disturbance is of maternal or fetal origin we cannot as yet definitely say.

Also previous observations concerning the chemical composition of marble bones have been confirmed in an uncomplicated case of this disease. The findings consist of hypermineralization, as indicated by a high ratio of inorganic to organic matter and an increase of the molecular ratio of calcium carbonate to calcium phosphate.

555 Prospect Place.

Case Reports

HYPERVITAMINOSIS A

JOHN A. TOOMEY, M.D., and RUSSELL A. MORISSETTE, M.D.
CLEVELAND

P. E., a 23 month old infant, was admitted to Babies' and Children's Hospital, Cleveland, on Dec. 22, 1944. The complaint was soreness and swollen legs.

Present Illness.—About Aug. 15, 1944, he fell. Soon afterward the right forearm became swollen and he complained of soreness along its radial aspect. On October 27, two days before admission to another hospital, a similar painful swelling began over the right shin which caused mobilization of the muscles of the right leg. He was irritable and anorexic. A tentative diagnosis of acute anterior poliomyelitis was made, but nothing was found to support it (J. A. T.). Roentgenograms of the bones showed them to be normal.

The child improved quickly, and within six days the pain and the tenderness disappeared, although a limp persisted. A possible diagnosis of acute periostitis was made. The patient received an indefinite amount of penicillin over a period of eight days.

Three weeks later (late in November) the signs and symptoms recurred, the involvement and the pain now being in both legs. He was readmitted to the same hospital on November 29 and was given penicillin therapy for six days, at the end of which time he was discharged. Repeated roentgenograms and blood counts revealed no abnormality.

One week later there was a second recurrence of pain and tenderness, this time in the forearms. In addition, he had anorexia, constipation and pruritus, and he was restless and irritable.

Past History.—The child had been breast fed, with supplemental formula feedings. Just before admission to Babies' and Children's Hospital he got meat, cereals and whole milk daily but no eggs or vegetables. The first twelve months of life he had no vitamin C, but had sufficient ascorbic acid since that time. He got from 1 to 2 teaspoons (from about 4 to 8 cc.) of cod liver oil daily from the age of 2 weeks. He stood at 7 and walked at 9 months.

Physical Examination.—The patient was normally well developed and was not acutely ill. His temperature was 37 C. (98.6 F.), his height 83 cm. and his weight 11,175 Gm. The anterior fontanelle measured 0.5 cm. by 1 cm. The skin of the face was erythematous, and there was roughening of the epidermis over the right leg; the lips were dry and cracked, and there was bleeding at the corners of the mouth. The hair was coarse, dry and sparse. There were a few nontender, discrete, movable shot-sized lymph nodes in the anterior, cervical and supraclavicular spaces. The chest was 46 cm. in circumference at the nipple line. The heart and the lungs were within normal limits. The abdomen was 49 cm. in circumference at the level of the umbilicus. The liver was palpable, its edges

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Read before the Section on Pediatrics at the Ninety-Fifth Annual Session of the American Medical Association, San Francisco, July 3, 1946.

From the Jack & Heintz Laboratory, Division of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University.

smooth and about 2 cm. below the right costal margin. There was no splenomegaly. Considerable tenderness was elicited when the femurs were palpated.

The blood and urine were normal, and reactions to tests done with old tuberculin down to a dilution of 1 to 100 were negative, as were reactions of blood serums on two occasions.

A determination of erythrocyte sedimentation rate (Westergren) showed a fall of 14 mm. the first hour and 35 the second.

Chemical determinations are listed in the table.

Laboratory Data for Patient with Hypervitaminosis A

Date	Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Phosphatase, Mg./100 Cc.	Serum Protein,* Mg./100 Cc.	Icteric Index	Nonprotein Nitrogen,† Mg./100 Cc.	Cholesterol, Mg./100 Cc.	Lecithin, Mg./100 Cc.	Total Lipids, Mg./100 Cc.	Vitamin A		Carotene, Mg./100 Cc.	Vitamin C, Mg./100 Cc.
										U.S.P. Units	Micrograms‡		
12/29/44	10.0	7.5	0.55	7.09	8								
1/ 4/45	10.4	4.5	0.55	6.9	5	..	...	...	...	200	67—	0	1.3
2/ 1/45	12.3	4.3	0.58	5.4	7	..	225	...	750	700	234—	Trace	0.9
2/20/45	....	...	....	....	..	21							
2/26/45	....	...	....	....	..	..	173	207	700	500	167—	Slight trace	1.0
3/ 8/45	11.6	4.3	0.83	....	..	..	180	219	533	800	267—	Trace	1.0
3/26/45	10.6	4.6	0.70	....	..	..	180	241	634	400	134—	0	0.5
4/19/46	12.2	3.4	0.69	4.9	..	..	195	235	883	1,200	400	0	
4/23/46	....	...	....	....	..	..	...	...	...	400	134—	0	
5/20/46	10.2	3.3	0.43	6.7	6	29	221	...	533	50	17—	0	

*Serum albumin, 5.1; globulin, 1.6; albumin-globulin ratio, 3:1 (normal 1.7:1 to 3:1).
† Creatinine, 1.1 (normal 1.2). Reactions to direct and indirect van den Bergh tests were negative.
‡ The U. S. P. units were translated by Josephs into micrograms, 1 microgram equaling 3 units.

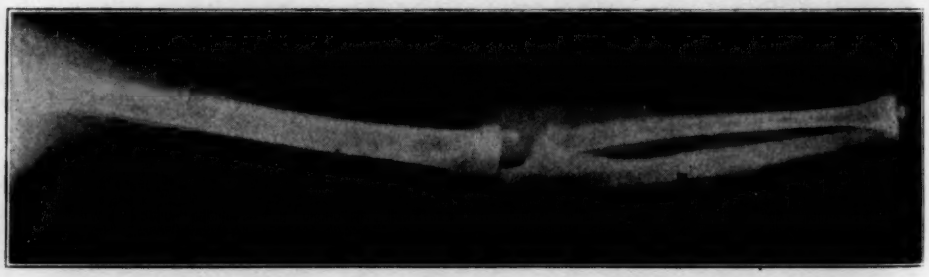

Fig. 1.—Roentgenogram showing condition in radius and ulna. Other roentgenograms of long bones were similar.

Roentgenograms of sinuses, the chest, etc., revealed no abnormality save for bilateral short cervical ribs. Those of the long bones revealed: (1) broad growth lines at the ends of all the long bones, (2) stippling of the distal femoral epiphyses, (3) fragmentation of the distal fibular epiphyses, (4) a periosteal line along the lateral aspects of the right femur and left tibia and (5) pronounced periosteal thickening on the posterior and the medial aspect of the ulnar bones. Stereoscopic roentgenograms of the skull were normal except for what appeared to be a minute foreign body in the scalp.

The course at the hospital was uneventful. After the first week he began to eat well, and a definite loss of weight was regained prior to his discharge. There was no diarrhea or vomiting; in fact, there were periods of constipation. The duration of the tenderness of the bones was about eight days. The skin remained essentially the same as described on admission.

He was discharged on the nineteenth hospital day with a diagnosis of probable healed or healing scurvy, and a high intake of ascorbic acid was recommended.

SECOND ADMISSION TO BABIES' AND CHILDREN'S HOSPITAL

On Jan. 31, 1945, three weeks later, he was readmitted. He remained in the hospital until April 23. The same symptoms were present, i. e., pain, swelling of the arms and legs and anorexia. At home and shortly after his previous discharge he had acute rhinitis, bilateral otitis media, swelling of the left eyelids and cervical adenopathy. On January 17 he contracted chickenpox followed by hematuria, which lasted about four days. Immediately before his admission, a red, dry rash had appeared around the neck folds. The diet during this period between hospital admissions had been limited almost exclusively to small amounts of milk, orange juice, preparations of vitamin D and various medications.

On examination, the lips were dry and fissured; there was peeling of the skin over the hands and feet, and there was left cervical lymphadenopathy.

Two days after his admission there was swelling of the skin in the neck folds and the skin of both shins. The child said that he felt "as if he had stones" in his shoes which made him walk on his heels. The stools were dark and tarry and contained fresh blood. About four days after admission he became more irritable than usual, was thirsty and drank a great deal and passed colorless stools. His mother thought that he favored his left leg and that he limped on that side.

She was cross examined about the boy's diet. He was the first and only child and of great concern to a conscientious mother. He was a "fussy eater," consuming no fruits and few vegetables. His customary daily diet consisted of some cereal, about 1 pint (473 cc.) of milk, 6 ounces (177 cc.) of orange juice, two tablets (25 mg. each) of ascorbic acid and 2 teaspoonfuls (8 cc.) of cod liver oil.

The patient appeared to be acutely but not severely ill. The temperature was 37 C. He weighed 11.8 Kg. The abnormalities noted were as follows: (1) healed varicella lesions; (2) mucopurulent crusts in the nares; (3) fissured and crusted lips which bled easily; (4) palpable nontender lymph nodes in the inguinal, axillary and left cervical regions; (5) a palpable nontender liver extending 2 cm. below the right costal margin and enlarged to the left nipple line; (6) an equisitely tender area (0.5 cm.) of swelling over the lower third of each radius, and (7) similar tumors over the lower third of each radius and over the lower third of both tibias, more obvious on the left. The swellings were not hot, shiny, erythematous or fluctuating and were in the bone structure rather than in the skin or the subcutaneous tissue.

The hemoglobin concentration was 85 per cent, the erythrocyte count 3,700,000 and the leukocyte count 15,400, with 41 per cent polymorphonuclear cells, 55 per cent lymphocytes and 4 per cent monocytes. The urine was normal. A leukocyte count of 23,800 was recorded on February 5, with the same proportions of the various types of cells as before. Platelet counts were 405,000 and 410,000 on two occasions, the bleeding time four and one-half minutes, the clotting time three to four minutes and the prothrombin time thirty seconds (control, twenty-nine

seconds). Serologic reactions of the patient and the mother were negative. Erythrocyte sedimentation showed a fall of 40 mm. the first hour. The chemical analyses of the blood are noted in the table.

The vitamin A level was 240 micrograms per hundred cubic centimeters. The method used to determine this was referred to by Josephs [1] as the method of Clausen and McCord and was described by him in detail. Josephs stated that roughly 50 to 60 U. S. P. units per hundred cubic centimeters may be taken as a level dividing normal from abnormally low.

His mother was requestioned about the vitamins she gave her son, and this time she admitted giving the following: (1) a preparation of vitamin B complex, 2 teaspoons daily; (2) 1 dicalcium phosphate capsule daily; (3) grains (325 mg.) of saccharated ferrous carbonate twice daily; (4) 50 mg. ascorbic acid daily, and (5) percomorph liver oil with viosterol (Mead),[2] 1 teaspoon daily from the newborn period until October 1944 and then 2 teaspoons daily until the time of admission. His symptoms began shortly after the vitamins had been increased. The last preparation noted had not been given during each hospital stay, and each time he got better. It was learned that the patient was abnormally fond of butter, which he would eat by the teaspoonful.

About eight days after admission the periosteal pain and the tenderness disappeared, although the swelling and the dry, scaly condition of the skin remained for three weeks.

First Clinical Experiment.—Domagk and von Dobeneck,[3] as well as Willstaedt [4] and others, describe a symptom complex in rats produced by feeding moderately large amounts of vitamin A concentrate. The hair falls out, the eyelids are sealed, exophthalmos appears, the liver is large and there are spontaneous fractures of the bones.

No similar changes were found when large doses of carotene were ingested by guinea pigs,[5] rats [6] and rabbits.[7] Josephs [8] has published a report of a case

1. Josephs, H. W.: Studies in Vitamin A: Relation of Vitamin A and Carotene to Serum Lipids, Bull. Johns Hopkins Hosp. **65**:112, 1939.

2. One teaspoon would equal approximately 250,000 units of vitamin A and 35,000 units of vitamin D. The information on the bottle is summarized as follows: "oleum percomorphum with other fish liver oils and viosterol, a liquid standardized to contain not less than 60,000 units of vitamin A and 8,500 units of vitamin D, U. S. P., per gram; approximately 1,250 vitamin A units and 180 vitamin D units per drop; source of vitamins A and D in which not more than 50 per cent of D is derived from viosterol."

3. Domagk, G., and von Dobeneck, P.: Ueber histologische Befunde bei der Ueberdosierung mit vitamin A-Konzentrat, Virchows Arch. f. path. Anat. **290**: 385, 1933.

4. Willstaedt, H.: Die Vitamine: Jetziger Stand ihrer Chemie und Biochemie, Klin. Wchnschr. **14**:841 and 1089, 1935.

5. Wells, H. G., and Hedenburg, O. F.: The Toxicity of Carotene, J. Biol. Chem. **27**:213, 1916.

6. Davies, A. W., and Moore, T.: Vitamin A and Carotene: The Distribution of Vitamin A in the Organs of the Normal and Hypervitaminotic Rats, Nutrition Abstr. & Rev. **4**:43, 1934.

7. Landy, M.: The Non-Toxicity of Large Amounts of Carotene, Department of Bacteriology, Ohio State University, unpublished data, 1934.

8. Josephs, H. W.: Hypervitaminosis A and Carotenemia, Am. J. Dis. Child. **67**:33 (Jan.) 1944.

with an excellent discussion on hypervitaminosis A and carotenemia, and a complete bibliography is included.

With his mother's permission, an experiment to reproduce the clinical symptoms was started on the twenty-seventh hospital day. The level of vitamin A in the blood had by this time fallen to 500 U. S. P. units, or about 170 micrograms, per hundred cubic centimeters. He was given the same therapy as at home. This therapy was discontinued after eight days, for by that time the patient had become increasingly irritable and his skin was oily, scaly, rough and pruritic. He had been given approximately 4,000,000 U. S. P. units of vitamin A and 560,000 units of D. There was an obvious soft swelling over the distal ulna, which was painful and exquisitely tender. The level of vitamin A in the blood was greater than 800 U. S. P. units, or about 267 micrograms, per hundred cubic centimeters. The total fats were increased.

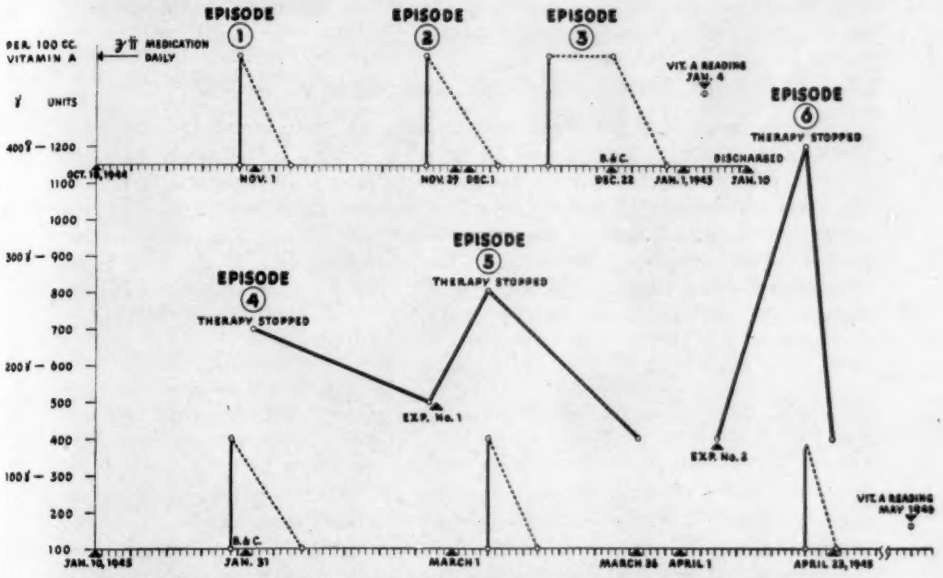

Fig. 2.—Chart summarizing case of hypervitaminosis A. The single solid line indicates the episode of pain, the dotted line the length of time the pain lasted and the double line the level of vitamin A in the blood.

As before, the symptoms and signs again disappeared about seven days after the vitamin therapy had been discontinued. The vitamin A level also fell at the same time and on March 26 was 400 units, or about 134 micrograms, per hundred cubic centimeters.

Second Clinical Experiment.—Was the condition of this patient caused by too much vitamin D? In this experiment he had received nearly 4,000,000 units of vitamin A, but he had also received over 500,000 units of vitamin D.

Again, with permission of the mother, an attempt was made to reproduce the syndrome, this time with a preparation which did not contain vitamin D.[9] One

9. A letter from E. R. Squibb & Sons contained the following information: "Vitamin A in oil is supplied in 1 cc. ampules, 100,000 units in each cubic centi-

(Footnote continued on next page)

hundred thousand units was given daily for the first four days and then the dosage was increased to 600,000 units daily. On April 19 tenderness appeared over the radiuses and tibias. The vitamin A level was greater than 1,200 units, or about 400 micrograms, per hundred cubic centimeters and, to my knowledge, the highest ever recorded. Administration of the vitamin A preparation was discontinued after fourteen days, a total of 6,200,000 U. S. P. units of vitamin A and less than 640 units of vitamin D having been given by this time. The total fats were again increased.

On April 23, the day of discharge, the vitamin A level was 400 units, or about 134 micrograms, per hundred cubic centimeters, and clinical signs and symptoms had practically disappeared except for a persistent hepatomegaly.

The roentgenologic observations were the same as previously, although the lines noted on prior admissions in the right femur and the left tibia could not be visualized. There was a periosteal thickening of the middle third of both ulnas. Bone age was neither advanced nor retarded.

THIRD ADMISSION TO BABIES' AND CHILDREN'S HOSPITAL

He was hospitalized the third time on May 20, 1946, for the purpose of a check-up examination. At this time he had acute rhinitis, but otherwise appeared normal. Neither the liver nor the spleen was palpable. The hair was luxuriant; the areas of previous cutaneous lesions had healed. There were a few infected papules on the dorsal areas of the left and the right wrist. The chemical composition of the blood was normal, and the roentgenograms of the long bones showed only those changes incident to growth. There was no evidence of hepatic damage. The vitamin A level was less than 0.5 U. S. P. unit per cubic centimeter.

COMMENT

To my knowledge, no toxic effects have ever been described following the ingestion of carotene. Josephs [8] stated that carotene is less well absorbed than vitamin A and that the interval taken for this conversion prevents flooding the body with active vitamins, which is necessary for the toxic effects. The highest value of vitamin A in over 700 cases in which tests were made by Josephs did not exceed 250 U. S. P. units, or about 83 micrograms, per hundred cubic centimeters. At one time the patient he described had 910 U. S. P. units, or about 304 micrograms, per hundred cubic centimeters. My case presented the highest figures which I have found on record—over 1,200 units, or about 400 micrograms, per hundred cubic centimeters. Subsequent experiments at home with large doses of carotene were not controlled enough to be reported, but there were no symptoms other than a definite carotenemia.

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meter. This product is a natural ester (distillate form). It is obtained from natural fish oils and is in reality concentrated through a molecular distillation process. The natural oils selected for each distillation contain extremely small amounts of vitamin D, usually considered negligible."

A second letter was received from E. R. Squibb & Sons regarding the amount of vitamin D. "We have no measure of the D content in the specific vitamin A distillate contained in these ampouls. At one time we tried to determine how much D was present in a vitamin A distillate. The results even of feeding at high dosage levels indicated that it was, well, what may be called negligible. In fact, it was not measurable at a dose set as low as 10 units per gram."

Was this patient's condition due to vitamin A or a combination of vitamins A and D, or was he conditioned by vitamin D to vitamin A or vice versa? The clinical picture as described by Josephs was reproduced in my patient by the combination of vitamins A and D, but the same symptoms and signs were also reproduced by vitamin A without vitamin D. The symptoms stopped sooner than one would expect if vitamin D were the offending factor; still one cannot be absolutely certain that vitamin D did not produce some additive effect.

Josephs stated that there is no "safeguard" against the zeal of a layman who is persuaded of the value of vitamins, but that the zone of safety between the prophylactic and the dangerous dose of vitamin A is so large that many cases may not be expected, but that cases doubtless will occur. It took six months before the vitamin A content of the serum in his patient was within the upper limit of normal. The phosphatase content of the blood was still elevated two and one-half years later; the liver was still palpable with firm, sharp edges 2 cm. below the costal margin; the spleen was a large firm mass and the fingers were slightly clubbed; the skeletal development was slightly in advance of chronologic age (7 carpal centers of ossification at 5½ years). My patient was completely well on May 5, 1946 (about twenty months after his first illness), and had no evidence of hepatic damage. A distinctive feature of this case was the rapidity with which pain was produced and the equal rapidity with which it disappeared.

SUMMARY

A case of hypervitaminosis A is reported the features of which agree with the observations set down by Josephs: (1) hepatomegaly (but no splenomegaly), (2) increased levels of vitamin A in the serum, (3) increased level of serum lipids, (4) abnormalities of bones, (5) increased level of serum phosphatase, (6) low level of serum proteins, (7) sparse, coarse hair, (8) avid appetite for butter, (9) abnormal intake of vitamin A and (10) prompt recovery after exclusion of vitamin A from the diet. To these we should be able to add (11) pain and localized periosteal swellings and (12) recovery from pain when the vitamin A was withheld.

3395 Scranton Road.

DISCUSSION

Dr. Edward B. Shaw, San Francisco: I am not so much amazed by the fact that mothers occasionally give enormous dosage of such substances containing vitamins as percomorph liver oil as by the fact that infants usually withstand this overdosage without symptoms. One of my friends in nursing used to say, "It all shows what the human body will stand." There are so many vitamin preparations with a multiplicity of names and with different dosages as to leave the mother with some confusion regarding the dose to be administered.

The recommended daily intake of percomorph liver oil is 4 drops, which is said to fulfil the average requirement. I measured out a teaspoon of percomorph liver oil yesterday using the standard dropper. It contained 150 drops, so that 2 teaspoons would contain 300 drops or in the neighborhood of seventy-five times the usual baby's requirement.

It occurs to me that a great many infants must be given a considerable overdosage of vitamin A and that in the case described by Dr. Toomey excessive dosage may have encountered extraordinary susceptibility on the part of the baby. It further occurs to me that some other factor may be entirely at fault.

I should like to point out the remarkable similarity, particularly regarding the bony changes, between this patient and a group of patients recently described

by Smyth. One member of this series is a patient whom I followed from the age of 6 months until the present, when he is about 3 years old. This child was presented with symptoms of discomfort resembling severe colic, and within the next little while soreness in his extremities developed which was thought to be due to scorbutic changes, although he was receiving some ascorbic acid. During the next few weeks, on adequate intake of ascorbic acid, swelling of both forearms and of both femurs and swelling about the mandible on both sides developed. There was no overlying redness, but the tenderness to pressure was even more pronounced than the swelling and there was striking resemblance to scurvy. This patient had an irregular low grade fever and a slight anemia but lacked the cutaneous changes, hepatomegaly and splenomegaly described by Dr. Toomey. Vitamin C levels in the blood were repeatedly normal and, most regrettably, the vitamin A levels were never determined. This child went on to slow improvement, which seemed to be accelerated by parenteral large doses of ascorbic acid, and he received generous, although never excessive, amounts of vitamins A and B. This case was one of a series presented by Smyth. A similar series has been presented from New York, in which utilization of ascorbic acid was thought to be the critical causal factor. There is enough resemblance between these patients to suggest a similar underlying cause. A further possibility, from which one could take off into the stratosphere of pure surmise, is that these symptoms might be provoked on one hand by faulty utilization of ascorbic acid and on the other by excessive amounts of vitamin A.

Dr. JOHN A. TOOMEY, Cleveland: The question is whether this child's condition was due to vitamin A, to vitamin D or to a combination of both vitamins A and D. I cannot state definitely whether there was some effect due to vitamin D. The patient experienced symptoms when he was given vitamin A plus vitamin D, but when he was given vitamin A only, he also had symptoms. The patient became better and improved when the vitamin A was excluded. In the last experiment he was given only a small amount of vitamin D, 640 micrograms, a negligible amount. Recovery from overfeeding of vitamin D is never so quick as was the recovery of this patient when vitamin A was withheld.

The patient had symptoms when given vitamin A again and got better when it was withheld, only to have the symptoms recur when it was fed again.

He had no disturbance of vitamin C at any time or subsequently. The symptoms of scurvy are recovered from quickly as in this condition, but when swelling of the periosteum is present due to scurvy, absorption takes longer than it did in this condition.

Our patient received no other vitamins while the experiment was in progress save ascorbic acid and the vitamin D in the preparation. I feel that in this particular instance there was no damage done to this child. I have never found any reference in the literature mentioning any reaction to carotene.

AGENESIS OF THE LUNG

With a Review of the Literature

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LITTLE ROCK, ARK.

AGENESIS of the lung is a rare condition as shown by a careful review of the literature. A certain amount of confusion has arisen, however from the loose usage of the terms "agenesis" and "aplasia." "Agenesis" has been used for conditions ranging from complete absence of the lung and main bronchus to those in which a variable amount of pulmonary tissue accompanies a rudimentary bronchus. It would be advisable to conform to the more precise usage of the terms and to use "agenesis" for a failure of development and "aplasia" for incomplete development. Schneider [1] has classified congenital defects of this kind into three main types: (1) true agenesis with no trace of the lung, bronchus or vascular supply on the affected side; (2) a type characterized by small outpocketing from the trachea with a rudimentary bronchus but no pulmonary tissue present, and (3) a type in which a fully formed bronchus is present but which ends in a fleshy mass of areolar tissue of varying amounts. This classification has been generally accepted.

Hurwitz and Stephens [2] in 1937 found 34 cases reported in the literature, and in 1944 DeWeese and Howard [3] added 9 other cases. An additional 11 cases have been found in the literature and are listed in the table. This gives a total of 54 cases, to which is added 1 case. Since the advent of bronchoscopy an increasing number of cases have been reported in living patients (Garber,[4] Ferguson and Neuhauser,[5] Stokes and Brown [6] and Widerman and Peters.[7]) Other cases were

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From the Department of Pathology, University of Arkansas School of Medicine Research Paper 834, Journal Series.

1. Schneider, P., in Schwalbe, E.: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1909-1913, vol. 3, pt. 2, chap. 8, p. 763.

2. Hurwitz, S., and Stephens, H. B.: Agenesis of the Lung: A Review of the Literature and Report of a Case, Am. J. M. Sc. **193**:81, 1937.

3. DeWeese, E. R., and Howard, J. C.: Congenital Absence of a Lung Diagnosed Before Death, Radiology **42**:389, 1944.

4. Garber, R. L.: Congenital Aplasia of the Lung, Am. J. Roentgenol. **53**: 129, 1945.

5. Ferguson, C. F., and Neuhauser, E. B. D.: Congenital Absence of the Lung (Agenesis) and Other Anomalies of the Tracheobronchial Tree, Am. J. Roentgenol. **52**:459, 1944.

(Footnotes continued on next page)

reported in foreign journals, unobtainable at the present time, by Mazzei,[8] Geissler,[9] Saxl,[10] Heemstra,[11] van Joost,[12] Formijne,[13] Purriel and Piaggio,[14] Pruys, Veen and Zuidema,[15] Wasmuht,[16] Bohnholtzer,[17] Marino,[18] Toro and Sa[19] and Lelong and Lemoyne.[20]

Data on Cases of Agenesis of Lung

Case No.*	Author	Sex	Age	Lung Absent	Observations
44	Mitchell, H. E.: Ohio State M. J. **32**: 950, 1936	F	2 yr.	Right	Right lung absent; left lung larger than normal, occupying part of chest on right side beyond midline; right main bronchus ended in a blind pouch; heart occupied lower two thirds right thorax; no pulmonary vessels found
45	Rienhoff, W. F., Jr.: J. Thoracic Surg. **6**: 254, 1937	M	50 yr.	Left	Small undeveloped left bronchus; left pulmonary vessels absent
46	Rienhoff, W. F., Jr.: J. Thoracic Surg. **6**: 254, 1937	M	4½ mo.	Right	Right lung and bronchus absent; patent interventricular septum; imperforate anus
47	Yampolsky, J., and Fowler, C. D.: Arch. Pediat. **55**: 293, 1938	M	2½ yr. (Negro)	Right	Heart displaced to right; only one lobe to left lung; weight of left lung 160 Gm.; right lung 12 Gm. and completely atelectatic; congenital stricture in main stem of right bronchus 1 cm. below carina; lumen at this point 1 mm. in diameter
48	Jamuni, A., and Ellis, A. G.: Am. J. M. Sc. **196**: 824, 1938	M	Premature (lived 1 day)	Left	Left side of chest lined with parietal pleura and contained fluid; rudimentary left bronchus; no pulmonary tissue
49	Killingsworth, W. P., and Hibbs, W. G.: Am. J. Dis. Child. **58**: 571 (Sept.) 1939	F	72 hr.	Right	Absent right lung; one lobe to left lung; no right bronchus or pulmonary vessels; absence of left kidney and ureter; only one ovary and fallopian tube
50	Choissier, R. M., and Bloedorn, W. A.: Internat. Clin. **2**: 243, 1939	M	43 yr.	Left	Adhesions in both pleural cavities; left lung 4.5 by 3 by 1.5 cm., a small fibrotic mass with small left bronchus; the left pulmonary artery was present
51	DeWeese and Howard[3]	M	6 mo.	Right	Diagnosed in life by bronchoscopy; right lung absent; mediastinum shifted to right; no bronchus on right; proved at autopsy
52	Valle and Graham[24c]	F	41 yr.	Left	Confirmed by exploratory thoracotomy; mediastinum displaced to left; absent left lung and pulmonary vessels; short left bronchial stump with no pulmonary tissue
53	Ferguson and Neuhauser[5]	F	4 mo.	Right	Right lung and bronchus absent; right pulmonary vessels absent; interstitial pneumonia on left; patent ductus arteriosus
54	Casaubon, A.; Cuculu, L. M., and Mosquera, J. E.: Arch. argent. de pediat. **24**: 3, 1945	F	5½ mo.	Left	Aplastic left lung 2 by 1 cm.; absent left pulmonary vessels; interauricular and interventricular septal defects

* The numbering of cases is a continuation of the tables begun by Hurwitz and Stephens[2] and continued by DeWeese and Howard.[3]

6. Stokes, H. L., and Brown, C. J. O.: Agenesis of the Lung: The Report of a Case, M. J. Australia **1**:49, 1940.

7. Widerman, A., and Peters, C. H.: Agenesis of the Lung, J. Pediat. **28**: 204, 1946.

8. Mazzei, E. S.: Pulmonary and Alveolar Agenesis, Tisiol. Univ. nac. de Córdoba, 1942, p. 233.

9. Geissler, J.: Unilateral Agenesia of the Lung, Zentralbl. f. allg. Path. u. path. Anat. **77**:339, 1941.

Agenesis is not incompatible with life, since patients have been reported dying from other conditions at 58, 65 and 72 years of age. The largest group of patients (23) given a diagnosis of agenesis of the lung were less than 1 year of age; of these 5 were premature or full term stillborn infants. Nine patients were between 1 and 10 years, while others were older. There were 33 cases of absence of the left lung and 21 of the right. Of 50 patients whose sex was given 26 were males and 24 females.

P. L. C., a Negro infant aged 2 months, was admitted to the University Hospital on April 26, 1946. The mother stated that there was failure of the baby to grow. The child was born at full term by a spontaneous vertex delivery after an uncomplicated labor of nineteen hours. The birth weight was 6 pounds and 3 ounces (2,806.6 Gm.). There was a large amount of mucus present in the throat of the infant at birth. No asphyxia or cyanosis was present. The baby nursed poorly during hospitalization. The mother previously had had several mentally defective children. The details about these children were unobtainable. During this last pregnancy the mother experienced hypertension (the pressure varied from 140 systolic and 100 diastolic to 165 systolic and 110 diastolic.)

The patient was seen by a physician on two occasions preceding the present admission to the hospital because of failure to gain weight and a persistent cough. She continued to nurse poorly. Physical examination on admission revealed a small, poorly nourished infant with a weak cry. Respirations were 38 per minute. The following salient features were found: A moderate amount of mucoid discharge was present in the throat. The chest was symmetric, and dulness to percussion was noted on the left. Some fine rales were heard over the right lower part of the chest posteriorly. The heart was regular in rhythm with no murmurs. The abdomen showed a distention which was tympanitic on percussion. There

10. Saxl, O.: Diagnosis of Agenesia of the Lung, Ann. pædiat. **154**:180, 1940.

11. Heemstra, T.: Agenesis of the Right Lung: Report of a Case, Nederl. tijdschr. v. geneesk. **83**:2750, 1939.

12. van Joost, C. R. N. F.: Three Cases of Congenital Anomalies in Children, Geneesk. tijdschr. v. Nederl.-Indië **79**:1155, 1939.

13. Formijne, P.: Agenesia and Hypoplasia of the Lung, Nederl. tijdschr. v. geneesk. **82**:5482, 1938.

14. Purriel, P., and Piaggio, A. A.: Agenesia of the Lung: Report of Cases, Arch. urug. de med., cir. y especialid. **14**:9, 1939.

15. Pruys, W. M.; Veen, R., and Zuidema, P. J.: Case of Pulmonary Aplasia, Geneesk. tijdschr. v. Nederl.-Indië **79**:398, 1939.

16. Wasmuht, K.: Hyperplasia of the Left and Total Agenesia of the Right Lung: Two Cases, Frankfurt. Ztschr. f. Path. **52**:519, 1938.

17. Bohnholtzer, E.: Unilateral Agenesia of the Lung, Beitr. z. path. Anat. u. z. allg. Path. **101**:614, 1938.

18. Marino, U.: Unilateral Agenesis of the Lung: Clinical and Roentgenological Picture, Rev. de tisiol. pract. **2**:120, 1936.

19. Toro, E., and Sa, A.: Congenital Malformations of Lungs, Rev. san. y asist. social **9**:1389, 1944.

20. Lelong, M.; Lemoyne, J.; Charousset and Lange: A Case of Congenital Absence of the Lung, Arch. franç. pédiat. **2**:31, 1944.

was a left inguinal hernia which extended down into the labium majus. The extremities showed no abnormalities. The clinical impression was of massive atelectasis of the left lung, malnutrition and an inguinal hernia.

The laboratory data were as follows: hemoglobin, 9.5 Gm.; red blood cells 3,210,000 per cubic millimeter, and leukocytes 17,750 per cubic millimeter, of which 68 per cent were polymorphonuclear leukocytes and 32 per cent lymphocytes.

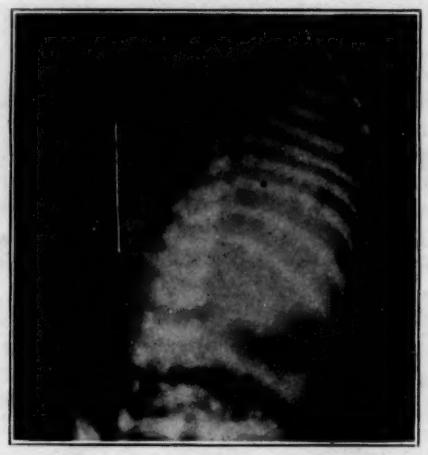

Fig. 1.—Roentgenogram of chest showing nonaerated left pulmonary field.

Fig. 2.—Photograph showing anterior view of thoracic contents and a portion of the left thoracic wall. The left lung is absent. The right ventricle is hypertrophied. Note that the pericardium is adherent to the parietal pleura on the left.

A roentgenogram of the chest showed a clear, well aerated right pulmonary field (fig. 1). There was a dense homogeneous opacity of the left pulmonary field with some shift of the mediastinum and its contents to the left. No pulmonary tissue could be seen in the left pleural cavity. The intercostal spaces were wider on the right than on the left.

Course in the Hospital.—The child fed poorly. Twelve hours after admission there was observed some difficulty in respiration which persisted until death the following morning.

Postmortem Examination.—Gross Observations: Only the pertinent pathologic changes are included in this report. The left pleural cavity was obliterated almost entirely by a complete absence of the left lung and a shift of the heart into the left side of the chest. There was an adherence of the pericardium to the left parietal pleura at the apex and along the left lateral thoracic wall as shown in figure 2. No fluid was found in the space of the left costophrenic angle. The right pleural cavity was filled by the right lung. The thymus gland was of normal size and

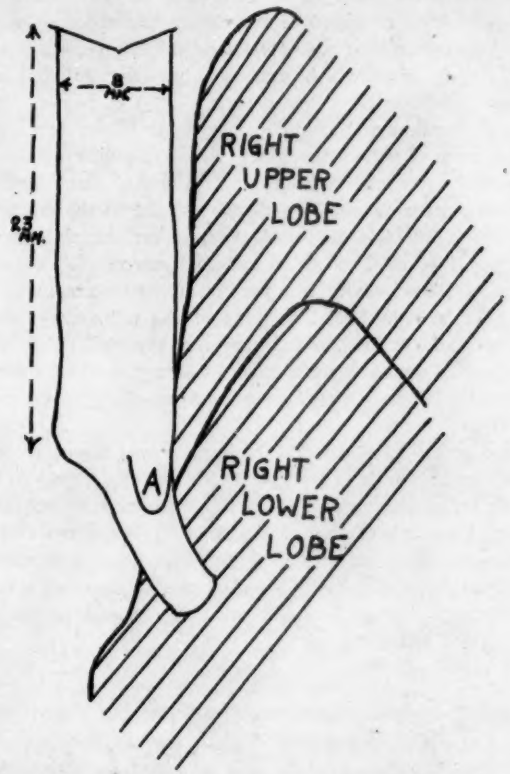

Fig. 3.—Diagrammatic sketch showing the posterior view of trachea and right lung which has only two lobes. The apical lobe is absent. *A*, the cartilaginous bud believed to represent the eparterial bronchus. Note that the trachea continues as the right main bronchus without bifurcating.

in normal position. The diaphragm showed no defects. The heart was enlarged, measuring 5.5 cm. across its widest portion. The right ventricle was hypertrophied and dilated. The right auricle was dilated. The left auricle and ventricle were normal. The ductus arteriosus and the foramen ovale were patent. The three main branches from the aortic arch arose in their normal position. A single pulmonary artery arose from the pulmonary trunk at a point 1.2 cm. above the pulmonary valve. This artery passed to the right lung and after penetrating the hilus divided

into two main branches. The pulmonary trunk measured 7 mm. and the aorta 5 mm. in diameter. Careful examination failed to reveal any traces of a left pulmonary artery. The venous return from the right lung emptied normally into the left auricle. There was nothing recognizable as the left pulmonary veins. The trachea descended to the left of the vertebral column and without bifurcating continued as the right main bronchus (fig. 3). The diameter of the trachea below the glottis was 8 mm. At the level where the bifurcation of the trachea is normally found there was a narrowing of the lumen to 5 mm. Approximately 3 mm. distal to this point of narrowing there was a small firm cartilaginous bud on the right main bronchus which measured 2 mm. in diameter (fig. 3). There were fifteen cartilaginous rings between the point of narrowing of the trachea and the cricoid cartilage. The right lung consisted of two lobes, the upper of which was heavy and congested. The lower lobe was atelectatic. There was a small hernial sac, 1.5 by 1 by 1 cm. in size, which extended into the left labium majus. No abnormalities were found in the other organs.

Microscopic Observations: Sections of the upper of the two lobes of the right lung showed well aerated pulmonary tissue with thickening of the alveolar walls. The bronchi showed an acute and chronic reaction. The blood vessels within the pulmonary tissue were normal. In the lower lobe of the right lung there was extensive atelectasis. Serial sections of the bud on the right bronchus showed that it was composed of oval pieces of cartilage surrounded by loose connective tissue. No epithelium-lined cavity was present, and no pulmonary tissue was seen in the sections of this bud. Serial sections of the pulmonary trunk made from the point of division did not reveal any defect in the wall of the vessel. Sections of the fused pericardium and parietal pleura showed a fibrous tissue layer lying adjacent to the skeletal muscle of the intercostal muscle. No layers of mesothelial lining were noted.

Anatomic Diagnosis: The anatomic diagnosis was agenesis of the left lung and the left bronchus; agenesis of the apical lobe and the eparterial bronchus of the right lung; single pulmonary artery (right); edema and congestion of the middle lobe of the right lung; atelectasis of the lower lobe of the right lung; patent ductus arteriosus and foramen ovale; hypertrophy and dilatation of the right ventricle and dilatation of the right auricle; displacement of the heart into the left side of the chest; adherent pericardium to the parietal pleura on the left, and inguinal hernia on the left side.

COMMENT

The embryology of pulmonary agenesis has been reviewed by Gruenfeld and Gray.[21] Ellis[22] suggested that the malformation of the pulmonary circulation is primary, followed by a failure of development of the pulmonary tree on the affected side. Other authors have assumed the reverse picture to be true; i. e., a failure of the stem bronchi to bud, or aplasia of the pulmonary tissue, either of which is followed by a failure of development of the circulation. In the case reported here there is an absent left lung and there are two lobes in the right lung with no eparterial bronchus; no left pulmonary artery is present and the right pulmonary artery continues directly into the hilus of the right lung to

21. Gruenfeld, G. E., and Gray, S. H.: Malformations of the Lung, Arch. Path. **31**:392 (March) 1941.

22. Ellis, A. G.: Congenital Absence of Lung, Am. J. M. Sc. **154**:33, 1917.

divide into branches which follow the bronchi. No pulmonary artery is found in the position where the eparterial branch for the apical lobe of the right lung would be expected. This follows the pattern of development reported in other cases in which the circulatory and the pulmonary defects match.

The primitive respiratory tube is believed to divide into the two main stem bronchi about the fourth week. The pulmonary arteries sprout from the so-called pulmonary arches the embryology of which is not clearly defined inasmuch as the six pairs of aortic arches developing in mammals are not all present at one time. The fifth pair are rudimentary and inconstant. Arey [23] stated that some prefer to call the arch that follows the suppositious fifth arch not the sixth arch but merely the pulmonary arch. The aortic arches develop through the fifth week, and their transformation into the major vessels occupies the sixth and seventh weeks. It has been said that the changes brought about in the arches are due not only to the loss or interruption of some arches and aortic segments but also to factors such as slowing of the flow of blood to various organs and to the enlargement of certain vessels and the new formation of others.

The importance of diagnosis in cases of agenesis and aplasia of the lungs during life has been stressed by many authors.[24] Agenesis of the lung is not incompatible with life, although associated congenital abnormalities are common. Young patients are prone to have dyspnea, cyanosis or harsh breathing, and they do not thrive as well as normal children. The thorax is usually symmetric although it may be flattened. Some degree of scoliosis may be present. Shifting of the mediastinum to the affected side occurs. There is usually either dulness or flatness of the percussion note on the affected side; occasionally resonance is present because of either hypertrophy or emphysema of the remaining lung. The character of the breath sounds is variable on the affected side; most frequently they are found to be absent, suppressed or bronchial in type. Roentgenograms of the chest show a dense homogeneous shadow on the affected side with a shift of the heart and the mediastinum away from the remaining lung; the intercostal spaces may be narrowed on the affected side with an elevation of the diaphragm. The most frequent roentgenographic diagnosis in these cases is massive atelectasis. This was suggested in the case reported here. Bronchoscopy may be of help especially if the defect is of type I of Schneider. Instillation of iodized poppyseed oil 40 per cent is of value in all three types of malformation.

23. Arey, L. B.: Developmental Anatomy, ed. 3, Philadelphia, W. B. Saunders Company, 1934, p. 210.

24. (*a*) De Weese and Howard.[8] (*b*) Ferguson and Neuhauser.[4] (*c*) Valle, A. R., and Graham, E. A.: Agenesis of the Lung, J. Thoracic Surg. **13**: 345, 1944.

In one case in which the bronchoscopic diagnosis was massive atelectasis with complete occlusion of the main stem bronchus an exploratory thoracotomy was performed, at which time the left lung was found to be absent.[24c]

Agenesis and aplasia are probably more common than the tabulated number of cases indicates. With the increasing use of modern diagnostic aids more cases are being diagnosed during life. When the differential diagnosis of an obscure pulmonary condition suggests massive atelectasis, especially in young children, abnormalities of the pulmonary tree should be carefully considered.

SUMMARY

A case of agenesis of the left lung is described in a 2 month old Negro infant. The literature is reviewed and the total number of reported cases is brought up to 55. These include cases of agenesis and of aplasia of the lung. It is suggested that a separation of these two types of congenital abnormalities should be made on the basis of Schneider's classification.

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Progress in Pediatrics

EFFECT ON THE ORGANISMS OF CHILDREN OF PRIVATIONS CAUSED BY THE SIEGE OF BUDAPEST

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THE SIEGE of Budapest, which lasted fifty-two days, caused the inhabitants privations of unparalleled intensity in the history of the world war which came to an end recently. The siege did not affect the whole city alike. Some districts were relieved of the blockade in a relatively short time, while others were compelled to suffer throughout the duration of the siege. Buda, situated on the right side of the Danube, in the mountainous district where the mad and fruitless resistance was organized, suffered through the entire fifty-two day period of the siege. The OTBA Hospital, one of the most up-to-date sanatoriums of Middle Europe, is situated in this area and after exactly one year of activity found itself in the midst of the siege.

The hospital, though the building was rather new, constructed according to the latest principles of medical science, was unable to meet the wartime demands because it was built in a prewar year, and no allowances were made for the eventuality of war claims on it when it was planned. Thus there is no provision for modern shelters and other structures that would afford security for underground hospital activity. The patients and the medical and nursing staff lived through the fifty-two day siege in improvised quarters.

As I wish to deal in this article with the effect of the privations on children's organisms, I shall outline only the conditions of the children's ward.

When Germany occupied Hungary and the air bombardment of Budapest began, the children, as far as possible, were transported to the country. After that there were not many children in the ward. Accordingly, there were sufficient places in the shelter for the number in the ward. During the air raid alarms, whether short or long, the overcrowded state was tolerable, because after an hour or two the children would be brought back to the spacious ward, but after the beginning of the siege the unhygienic condition which of necessity prevailed caused disquieting anxiety.

From the OTBA Hospital; chief physician: Dr. Géza Gerloczy, professor at the University of Budapest.

EXPERIENCES DURING THE SIEGE

During close to two months of the siege, the narrow shelter of the children's ward was occupied by 33 children and 15 adults. The grouping of children, according to their ages, was as follows:

Younger than 1 year old; i. e., infants	12
Between 1 and 3 years	9
Over 3 years	12

The crowded state is best illustrated by the fact that 6 of the children, less than 3 years old, were placed, sitting or lying, across a full-sized bed. The infants were placed in similar fashion on a rather large child's bed, and 2 prematurely born babies had places in a basket. The adults used to sleep on litters, placed one above the other. Some of the mothers were compelled to share their beds with their babies, for whom a resting place could not otherwise be secured. Between the resting places there was just enough clear space for one person to walk. In the corner of the shelter there was a latrine, separated only by a thin brick wall, with every advantage and disadvantage of this proximity. The lighting of the shelter was provided by a petroleum lamp, but owing to the lack of petroleum the more primitive tallow tapers were often used. In the corridors the air was cold, damp, smoky from oil and petroleum lamps and irritating to the mucous membranes. Inside the shelter, the only difference was that the crowded state diminished the coldness and increased the offensive odor.

Before I give full details of the effects of privations, I shall differentiate between two groups of children, from a medical standpoint. The first group contained those who spent the time of the siege in the shelter of the children's ward and were observed continually. To the second group belonged those who were able to come to the hospital only after the siege. This distinction seems appropriate, because the way of living of the children belonging to the first group was rather similar, whereas for the second group the living standards varied with different periods as to nourishment, lack of sunshine and the crowded state in which they found themselves. The latter group, in other words, lived through the siege in different parts of the city, some of them inside the ring of the blockade under difficult circumstances, while others lived farther from the scene of battle. In order to survey the effect of this rare accumulation of disadvantageous hygienic conditions, one should become acquainted with the elements of the living conditions of these children. One must take into consideration (*a*) the food, as to quality and quantity; (*b*) the duration of the lack of sunshine, and (*c*) the crowded state.

With respect to the food, one can say that in the first as well as in the second group those infants first met privation who were put on a

diet of cow's milk, even before the siege, because of a lack of mother's milk.

At the beginning of the siege, shipments of milk from the country stopped. Powdered milk is not manufactured in this country at all, and infant food containing cow's milk is produced only in small quantities. Thus the inhabitants had practically no reserve supply of milk, while food containing cow's milk was acquired only in exceptional cases and by few persons. This milk deficiency caused, as will be seen, the greatest harm among the infants.

The first group, i. e., the infants living in the shelter of the hospital, still received 2,000 to 3,000 Gm. of milk during the first week, made possible by the supply left from the shipments which had arrived for Christmas. (It was on Christmas day that we were to go down to the shelter, which we were not able to leave until February 13.) When the supply was exhausted, the hospital was short of milk for three months—from January 1 until the end of March. Having no milk, my colleagues and I were obliged to make up food, as rational as possible, from the artificial food in stock. This contained 1,000 Gm. of water, 100 Gm. of crystalloid carbohydrate, 50 Gm. of decoction of rice (200 calories), 20 Gm. of sugar (80 calories) and (in 10 Gm. of Caphosein) 8.5 Gm. of albumin (30 calories). The total calories were 710. In the 10 Gm. of Caphosein there was also 0.24 Gm. of calcium oxide and 0.17 Gm. of phosphorus pentoxide. As may be seen, in regard to number of calories this food was satisfying, but naturally it was not satisfying from a biologic point of view. We endeavored to supply the biologic deficiencies, partly at least, with vitamins. The infants who were nourished artificially (without mother's milk) received daily 100 mg. of ascorbic acid, 2 mg. of thiamine and 10,800 international units of vitamin D_2. Those who were nourished partly with mother's milk received smaller doses of vitamins; we knew that the doses of vitamins were not sufficient, but we had to be economical because there was no hope of getting replenishments. We gave 200 Gm. of the formula described three times a day and 150 to 200 Gm. of vegetables twice a day to the infants 5 months old or older. The 2 prematurely born children were kept on mother's milk and provided with vitamins as has been described.

The children between the ages of 1 and 2 years got the same food, except that their portions were larger, according to their ages. The vegetables consisted of potato, carrot, canned French beans and dried peas. The children over 3 years old got about the same food as the adults. Toward the end of the siege it began to become monotonous, because it was almost always thick soup consisting of strained peas and beans. There was no lack of lard, but we did not dare to take any chances with this on account of the danger of catarrh.

The infants were without sunshine for six weeks and the other children for fifty-two days. The crowding, as I have described, was extreme.

The children staying in the hospital shelters were divided, according to their state of health, into three categories: (1) the healthy, (2) the slightly sick and (3) the seriously sick children. Of the seriously sick children one had pulmonary tuberculosis, another desquamative erythroderma and another bronchopneumonia.

The 2 infants nursed by their own mothers did not suffer any remarkable losses. Their turgor was good, the color of their flesh was like a faded rose and their increase in weight was satisfactory. On the other hand, the 2 prematurely born children (one of them 7, the other 8 weeks old) soon lost their appetite. They had been developing nicely in the ward, but down in the shelter the loss of appetite was followed by greater vacillation in weight and by stagnation. Slowly and gradually they became dystrophic, without having essential parenteral infection. It is worth noting that during the cellar life they got only mother's milk, because they did not thrive on other food. Nevertheless, the more serious form of dystrophy, decomposition, developed, and one of them died in the fourth, the other in the ninth month of life. Four infants subsisted on the formula containing Caphosein, rich in carbohydrates, plus vegetables twice a day. Their development was not satisfactory, although no enteral or parenteral injury which might endanger their lives resulted. They were characterized by moderate hypotrophy, paleness, bulging abdomen and diminished turgor. Their appetite and agility remained. After the siege, all of them were taken to the country in order to get milk.

When we had the presentiment that we would be forced into cellar life for many weeks, we anxiously anticipated influenzal infections and their consequences.

The adults living in the shelter of the children's ward were obliged to carry water and do other work. As it was winter and cold, they caught cold and had colds and coughs. Besides, it was impossible to avoid using the latrine in the shelter, and because of this the shelter for the children's ward was visited both by patients and by other persons who did not belong in our ward. Prophylactic measures, such as wearing of masks, became impossible to carry out. In spite of this, no serious epidemic of influenza occurred. Only a mother and her 2½ year old child had considerable fever in a rather serious angina. Since their separation was impossible, they lay in their place in a most crowded spot. Notwithstanding this, their illness was not caught by others. Both showed a considerable tendency toward lymphatism.

There was much alarm caused by a case of typical scarlet fever, contracted by a 3 year old child on the fifth day of the siege. The manifestations in throat and skin were unmistakable, and the diagnosis was

confirmed by the desquamation which began three weeks after the first manifestations. No precautionary measures were taken, because we had no convalescent serum and the making up of serum from adults for so many children was also impossible. I must remark that our city had been surrounded so suddenly that preparation for siege life had been impossible. We had only time to carry down to the shelter the most indispensable things, risking our lives at the same time. There was no opportunity to isolate the patient with scarlet fever, so that the acute and the desquamative phase were passed there in that crowded place. The child was one of the 6 lying close together across a bed for adults. This case was not followed by any others. In this connection, one may justly ask whether scarlet fever is really such a contagious disease as is assumed by the textbooks. How does it spread? Surely every condition for contagion was present—and redoubled. Was not Professor Szontagh right in referring to the problems of scarlet fever?

The case of meningitis was not cleared up etiologically, because the bacteriologic examination of cultures was not in our power. Setting aside the clinical symptoms, I mention only the data on the spinal fluid. The fluid was slightly yellowish, evacuating with medium pressure and having 288 mg. of globulin per hundred cubic centimeters and 56 mg. of sugar. After a few days the number of cells decreased to 64. There was a good response to preparations of sulfapyridine. There was no possibility of other than a presumptive diagnosis, that it was aseptic or meningococcic meningitis. In any case, infection did not spread to any other patient from this case.

Still greater was our anxiety to see that the condition of a 1½ year old child with pulmonary tuberculosis was becoming constantly worse and that the child was perhaps the source of serious infection. Besides the continuous wasting away. auscultation indicated that the condition of the lungs was also becoming graver. After the siege the child was taken home and died there after two weeks. Five of the children, who spent more than seven weeks with him in the shelter, are still under my observation. Now after a year, there is no trace of tuberculous infection among them. (The Pirquet and the Mantoux reaction [a dilution of 1:1,000] were negative.)

On the last day of the siege the 11 month old daughter of one of our colleagues died. There had been a long period of dystrophy. During the last two weeks the signs of bronchopneumonia were observable, and, as her previous development was also not satisfactory and in the shelter her dystrophy became rapidly worse, we supposed tuberculosis to be present. The dissection and the histopathologic examination, however, excluded tuberculosis. We were convinced that she was a victim of the cellar life, because under normal conditions in a ward she could have been saved.

EXPERIENCES AFTER THE SIEGE

On Feb. 12, 1945 the city fell. We were set free from the nightmare of the long siege, but the saddest phase of our medical activity still was before us. After the siege, the infants, who were in the worst condition, were brought in every day; we could take in only a limited number of patients on account of the shortage of space.

The children who were brought in were suffering from severe malnutrition, as a consequence of the scarcity of food. Milk, representing animal albumin, was lacking everywhere. The hospital also was without a supply of it, and other articles were lacking too. Daily 500 to 600 Gm. of mother's milk was at our disposal, but this seemed inadequate in the face of the immense needs. We admitted the patients to preserve the last hopes of the parents, but we ourselves had no doubt about the outcome.

To illustrate the quality of food provided for the children living outside the hospital during the siege, I include the following data:

1. Paul B. G. and Peter B. G., 8 month old twins, were both in a serious condition, one having bronchopneumonia and the other feverish bronchitis. For six weeks they received only 250 Gm. of watery Rizomaltan (dextrose-maltose preparation) three times a day, 200 Gm. of watery porridge once a day and 200 Gm. of strained carrot once a day.

2. Ladislas Sz., 3½ months old, for four weeks received 150 Gm. of thick soup four times a day and 150 Gm. of watery porridge once a day. His face and feet were edematous. His body was lean. He was apathetic.

3. Ferdinand L., 4 months old, nursed for three months. For a month he received only flour soup and Rizomaltan in water and porridge. He had ctitis media and was seriously malnourished.

4. George S., 6 months old, for a month got no milk and received only flour soup and porridge, boiled in water. He was admitted to the hospital on account of serious malnourishment and pyoderma.

Such was the food of the great majority of infants. It was an extraordinary case if here and there a mother could add some preparation containing cow's milk to the vegetables boiled in water, but the majority could get no milk for weeks.

In consequence, children with serious malnourishment came day by day before our eyes. We have seen in large numbers infants with the serious forms of atrophy and decomposition. Patients with typical injury from a diet with too high a proportion of carbohydrates (Mählner disease) came by scores, though this illness had nearly vanished in Hungary. The few rooms which were at our disposal were filled with infants, wasted in different degrees, but principally being nothing but skin and bone. The subcutaneous fatty tissue was completely gone; the face, the trunk and the limbs were covered with skin folded into wrinkles and folds. The individual features of the infant disappeared,

and everywhere the same suffering old faces looked at us from the little beds.

In respect to pathogenesis, we were faced with forms of malnutrition in which the course of the illness can almost be called irreversible. It is known that this serious form of inanition results when the metabolism of the young organism does not accommodate itself to the poor provision of calories, but the oxidative processes remain on the normal level, even increasing. The tolerance continually becomes narrower, so that the food causes a decrease instead of an increase in weight. The seriously dystrophic child consumes the substance of its own body. The intermediary metabolism proceeds in reversed direction; it dissimilates instead of assimilates. The illness in the cases of most serious disease may become irreversible. Clinical experiences, however, show that the irreversibility cannot be determined exactly. We know that of the infants judged to be in a most serious state one or more can sometimes be saved.

As may be seen, the course of illness is affected by the resources for therapy. The prognosis for infants with marasmus is doubtful, even under ideal circumstances. Besides mother's milk, one must make use of the whole capacity of the milk kitchen. We mostly suffered from the lack of milk—this most important therapeutic component. Our next aim, therefore, could be nothing more than to gain time until we could obtain milk. For this it seemed most advantageous to use transfusions, from which we hoped to supply, at least partly, but in a most appropriate way, the albumin which was lacking, and to heighten the immunity. We combated the great losses of weight with infusions of isotonic solution of sodium chloride plus 5 per cent solution of dextrose.

The acquisition of milk, nevertheless, involved such great hardship that we were compelled to pass this heavy task to the parents. In this field we saw heroic achievements. The emaciated and weakened parents walked kilometers day by day for a few deciliters of milk. For about six weeks this heroic struggle lasted, because that much time passed, during the great disorganization in the city, before the provision of milk was to a certain degree organized by the authorities. In many cases, however, cow's milk did not give hope for recovery; therefore parents had to hunt up some mother's milk. A touching example of generosity was given by a Red Cross nurse. For three months she collected mother's milk from three or four distant parts of the city for a 4 month old infant, who had lost both parents.

There was a contest in which parents and physician struggled, shoulder to shoulder for the life of each child. Still we lost many battles. The balance is as follows:

From Feb. 15, 1945 until August 1, 139 children were admitted to our ward. Thirty-five died, which means a mortality of 25 per

cent. However, if the condition of children of less than 1 year of age is examined, the horrifying effect of the privations caused by the siege becomes evident. Among the 139 children there were 65 younger than 1 year. Of these 28 died, or 43 per cent.

Twenty-eight of the 65 infants suffered from other complications besides the shortage of food. Of these 11 died, representing 52.4 per cent.

SUMMARY

During the life in the shelter, which lasted two months, in spite of the crowding no epidemic of influenza occurred. On the fifth day of life in the shelter a typical case of scarlet fever developed. This was not followed by other cases. The development of the infants fed on mother's milk was satisfactory except for the 2 prematurely born infants, who died.

It was observed, with respect to the children brought to the hospital after the siege, that children less than 1 year old were most seriously affected and that there were numerous cases of extreme malnutrition. The cause of the malnutrition was the lack of milk. As a result of the privation, during the months following the siege infant mortality rose to 43 per cent, which exceeds the mortality during the most serious epidemic.

Abstracts from Current Literature

Vitamins; Avitaminoses

THE INDUCTION OF VITAMIN C SUBNUTRITION: A COMPARISON OF INTRADERMAL TESTS WITH PLASMA ASCORBIC ACID LEVELS. LAWRENCE B. SLOBODY, REUEL A. BENSON and JOAN MESTERN, J. Pediat. **28**:134 (Feb.) 1946.

Vitamin C subnutrition was induced in 16 children by means of a diet which lacked citrus fruits and tomatoes. The levels of ascorbic acid in the plasma and the results of intradermal tests followed reliably the induction of vitamin C deficiency and returned to normal with administration of ascorbic acid.

The authors' intradermal test is cheap, easy to perform and quickly read. The test is based on the intradermal injection of a dye which will be decolorized by vitamin C. Slow decolorization of the dye would indicate that the tissues have an insufficient amount of vitamin C. Rapid decolorization would indicate a sufficient amount. In their test enough of a three hundredth-normal solution of sodium 2,6-dichlorophenol indophenol is injected to raise a wheal approximately 4 mm. in diameter. When the length of time required for the dye to disappear is fourteen minutes or more a definite degree of tissue unsaturations is suggested; from ten to thirteen minutes is borderline, and less than nine minutes indicates that there is a normal amount of vitamin C in the body tissues.

In vitamin C subnutrition there are no clinical sign or symptoms of scurvy. The diagnosis can be made only by the history and the laboratory observations. In the history one looks for the four frequent factors in the production of vitamin C subnutrition: (1) an inadequate dietary intake of vitamin C, (2) a faulty absorption as in diarrhea and persistent vomiting, (3) an increased demand because of an increased metabolism, as in hyperthyroidism and prolonged febrile diseases and (4) an increased urinary excretion which has washed out the ascorbic acid, as in large intravenous infusions before and after operations.

AUTHORS' ABSTRACT.

COMPARISON OF ABSORPTION OF VITAMIN A AFTER ORAL AND INTRAMUSCULAR ADMINISTRATION IN NORMAL CHILDREN. GONZALO CIENFUEGOS, J. Pediat. **28**:191 (Feb.) 1946.

The parenteral administration of vitamin A has been widely recommended and used in cases in which steatorrhea has prevented normal absorption of vitamin A given orally, especially in cases in which there is fibrocystic disease of the pancreas. Clinical results following parenteral administration of vitamin A have been disappointing, however. In the present study a comparison has been made between absorption of vitamin A following oral and parenteral administration of the vitamin in 7 children without digestive symptoms. The levels of vitamin A in the serum rose normally after oral administration but showed little or no rise after intramuscular injection of the same preparation.

AUTHOR'S ABSTRACT.

LACUNAR SKULL OF THE NEWBORN. KATO VAN LEEUWEN, J. Pediat. **28**:193 (Feb.) 1946.

Lacunar skull is an anomaly of the skull of the newborn infant characterized by multiple defects of the inner table of the vault. These defects may vary in size, shape, number and extent. They are usually, but not invariably, associated with spina bifida, encephalocele, meningocele or myelocele. Other congenital developmental anomalies may be present. Hydrocephalus occurs frequently and may be progressive.

Baby H. was delivered by cesarean section (because of a large uterine fibroma) from a 40 year old, white primigravida whose Wassermann reaction was negative. A roentgenogram taken five weeks before delivery showed that the head of the fetus was enlarged. Increased lordosis was noted. The weight of the infant at birth was 7 pounds, 4 ounces (3,289 Gm.) and the length was 19 inches (48.3 cm.). The circumference of the chest was 13 inches (33 cm.), with the anteroposterior diameter slightly increased. The circumference of the head was 15 inches (38.1 cm.) in the occipitofrontal plane. The cranial bones were floating and their outlines easily palpated. Fine ridges were felt in the cranial bones, especially in the occipital and the parietal region. Soft areas were palpated over the entire skull. A large spina bifida with a meningomyelocele, measuring 4 by 5 cm., was present in the thoracolumbar region. The motion of the left leg appeared definitely decreased from normal. The Moro reflex was present. No pathologic reflexes could be demonstrated.

The cranial bones were extremely thin with thicker ridges running through them in a network, giving the appearance of multiple holes. The suture lines were wide. The spine, in the lumbar area, showed several hemivertebrae and a pronounced spread of the laminas.

The skull increased gradually in size. The protrusion of the dura through the defects in the vault became greater. The meningomyelocele, which was slightly depressed at birth, began to bulge by the second day, and seepage of the spinal fluid was noted. The subsequent course was downhill. On the seventh day, diarrhea and regurgitation became prominent. Hyperpyrexia occurred on the ninth day, and the baby died on the eleventh day with convulsions and other signs of meningitis.

At necropsy the bony plates were found to be extremely thin. Multiple defects, some of them surrounded by thick, sharp, bony ridges, others by thin, flat ones, were present and covered only by a translucent membrane consisting of dura and periosteum. There was a lacework of bony ridges visible at the interior aspect of the skull.

Vogt and Wyatt reported that 43 per cent of 120 patients with meningocele showed lacunar skull. Two cases of true lacunar skull were found in over 5,000 cases without meningocele. Lacunar skull occurred most frequently in association with thoracic meningocele and was least frequent in the presence of smaller meningocele. This incidence is higher in association with myelomeningocele than with the simple meningocele.

Hartley and Burnett, in Great Britain, gave an incidence of 0.94 per cent in 3,828 newborn infants and an incidence of 4.3 per cent in 232 fetuses of which roentgenograms were taken. Diagnosis rests on the roentgenographic appearance, unless there is an extreme case of lacunar skull.

AUTHOR'S ABSTRACT.

CORNEAL ULCERS FROM AVITAMINOSIS A. A. AGUIRRE, Bol. méd. d. Hosp. inf., México **1**:67 (March) 1944.

J. S. M., a 7 month old boy, was admitted with the complaint of "swelling" of the body of one month's duration. It had begun on the feet, then had spread to the legs and, finally, to the hands and the face. At the same time, the eyes had become injected and purulent. Since the age of 1 month, the only food the patient had received was rice gruel, without milk, but with a few drops of lime juice added.

At the physical examination the eyes were found to be congested, with pus. In each eye, in symmetric sites of the lower internal quadrant of the cornea, there was an ulcer that comprised almost all the corneal layers, to such a degree that the aqueous humor, on the right side, was herniated.

The patient died thirty hours later, but it was not possible to obtain permission for an autopsy.

MADERO, México, D. F., Mexico.

Prematurity and Congenital Deformities

ARACHNODACTYLY: UNUSUAL COMPLICATION FOLLOWING SKULL INJURY. W. F. SCHNEIDER, J. Pediat. **27**:583 (Dec.) 1945.

Arachnodactyly is an unusual clinical syndrome first reported by Dr. Marfan in 1896. Although only about 200 cases have been reported, renewed interest in such congenital defects should be aroused by recent investigation of related defects in babies whose mothers had rubella during the pregnancy; these defects have included cataracts, deaf-mutism, cardiac disease, microcephaly and mental retardation.

The unusual "spider hands and feet," the multiple ocular defects (in 50 per cent of the cases), the thinness of the extremities as opposed to the good subcutaneous layer of the trunk and the relaxation of the ligaments of the joints should suggest the diagnosis. Congenital heart disease has been found in 30 per cent of the cases. Abnormalities in the lobes of the lungs, retardation of sexual development and mental deficiencies are not infrequently found. The commoner ocular abnormalities are bilateral dislocation of the lens associated with tremulous irises, in 62 per cent of the cases, myopia, shallowness of the anterior chamber, miosis and strabismus. A comparison of Marfan's syndrome with the Laurence-Moon-Biedl syndrome has been suggested because of certain ocular changes and diencephalic disturbances.

The case of a 13½ year old white girl with arachnodactyly is reported. Mental retardation was evident during infancy and early childhood. Orthopedic correction of abnormalities of the bones and joints was begun in early life, but correction of the ocular defects was not undertaken. Progressive loss of vision led to an accident two years previously which gave rise to bilateral glaucoma. The ocular defects and mental retardation at approximately the 5 year level prevented efforts to obtain educational facilities for this patient.

The author points out the need for orthopedic and ocular corrections as early as possible to preserve such psychobiologic capacities as may be present. Likewise continued investigation of possible avoidable toxic factors during pregnancy should be continued to prevent such social maladjustments as occur in this syndrome.

AUTHOR'S ABSTRACT.

THE DEFINITION OF PREMATURITY. J. L. HENDERSON, J. Obst. & Gynaec. Brit. Emp. **52**:29 (Feb.) 1945.

The author discusses the desirability of adapting an arbitrary minimal weight standard for viable premature infants. Minimal weight standards in use vary from 1,000 to 1,500 Gm. The average weight of infants of 28 weeks' gestation is between 3 and 2½ pounds (1,307 and 1,134 Gm.). A minimal arbitrary weight standard for premature infants of 2¾ pounds (1,247 Gm.) is proposed. The term "previable" has been proposed for the separate category of premature infants with a birth weight of less than 2¾ pounds.

CUMMINGS, Evanston, Ill.

FUSED TWIN MONSTER. NORA L. KEEVIL, J. Obst. & Gynaec. Brit. Emp. **52**:513 (Oct.) 1945.

The author reports a normal delivery of a fused twin monster at term. The pregnancy was normal except for toxemia and polyhydramnios. Double monsters are rare, perhaps 1 in 25,000. The ratio of all twins to single births is 1 to 85. Double monsters are rarely born alive because of the mechanical difficulties of delivery. The author is inclined to accept the theory of polysperm as the cause of the monstrosities. If two fertilizing spermatozoa gain entrance to the ovum, two primitive streaks may be looked for. The relation of the two streaks will determine the relation of the future twins.

CUMMINGS, Evanston, Ill.

A NEW SYNDROME: MANDIBULOFACIAL DYSOSTOSIS. A. FRANCESCHETTI and P. ZWAHLEN, Bull. d. schweiz. Akad. d. med. Wissensch. **1**:60, 1944.

A particular congenital malformation of the inferior maxilla of the face is described for which the authors propose the name "mandibulofacial dysostosis." The syndrome is characterized by the following peculiarities: (1) slanting eyelids, the outer third sloping downward; coloboma of the upper and lower lids; (2) hypoplasia of the cheek bones and the lower jaw bone; (3) malformation of the auricle of the ear; (4) macrostomia and blind fistula between the mouth and the ear, and (5) abnormal position of the teeth and growth of the hair and Ogival palate.

The authors were able to observe an atypical case as well as a case presenting the complete syndrome. The part played by hereditary factors is especially stressed.

AUTHORS' ABSTRACT.

Newborn

CORD TRANSFUSIONS IN NEWBORN INFANTS. HARRY W. MAYES, J. Pediat. **28**:69 (Jan.) 1946.

After a long labor, a difficult forceps delivery or a breech extraction infants are frequently in severe shock which may or may not be accompanied by hemorrhage. In premature babies there is a low content of vitamin K and prothrombin, and hemorrhage accounts for the deaths in a large number. Taking these facts into consideration, the author began giving these babies cord transfusions as soon as possible after birth. The work was experimental at first, but after using the technic for four years and having given over three hundred cord transfusions the author is of the opinion that the blood does not harm the baby and that almost without exception the baby is benefited if the mother's blood is used. If other blood is used there may be a reaction and the condition of the baby may be made worse instead of better.

The blood should be withdrawn under sterile technic before the baby is born. Seven or 8 cc. of a 2 per cent solution of sodium citrate should be drawn into a 50 cc. syringe and the entire inside of the syringe moistened with the solution.

The amount of blood given depends on the weight of the baby and the reason for which it is used. As a rule the average amount should not exceed 10 cc. per pound (22 cc. per kilogram) of baby weight. Usually a little less than this amount is given.

It is preferable to inject the blood before the baby is separated from its mother. As soon as the baby is born it is either placed on the abdomen of the mother or it is held with its head down by an assistant. The cord should be clamped as far from the baby as possible and then the cord is held with a sponge in the left hand, while the barrel of the syringe is grasped with the right hand. With a large Fordyce needle on the syringe, the vein is carefully entered and the plunger forced in by making pressure on the plunger with the chest. If the injection is made 12 inches (30.5 cm.) or more from the baby and fails, another attempt may be made nearer the baby. Delay in making the transfusion may make it difficult or impossible.

At times it is advisable to separate the baby from its mother before the blood is given. When the cord is cut it is likely to collapse, so that the veins are hard to identify. If the cord is milked toward the clamp, enough blood can be collected to distend the vein.

Ninety-four premature babies received cord transfusions, with the loss of 15 babies. Six of these weighed less than 3 pounds (1,307 Gm.), and 9 were of less than 28 weeks' gestation.

Twenty babies were given transfusions after long labors or difficult deliveries with no deaths.

The blood was grouped and the Rh factor determined for 1,910 women during 1944. Of these 294 were found to be Rh negative, and 137 were delivered during

1944 with the loss of 4 babies, 2 in the group of 78 who received cord transfusions and 2 in the group not given transfusions. The 2 who died in the group given transfusions were premature, while the 2 who died in the group not given transfusions had some dyscrasia of the blood. One was jaundiced and the other had 158 normoblasts to 100 red blood cells.

Three infants in the group given transfusions, who were thought to have some form of erythroblastosis, all lived while 2 of the 5 infants with erythroblastosis in the group not given transfusions died.

During 1944 the author and his colleagues gave transfusions to primiparas as well as to multiparas, but in 1945 they gave transfusions mostly to those who had had a miscarriage or had borne children. They had several cases in which infants had erythroblastosis when they received the blood from their Rh-negative mother, but the infants have all recovered. In 1 interesting case the mother was not known to be Rh negative and the baby was given 90 cc. of maternal blood on the second day; later it was found that the mother was Rh negative, her blood having an exceptional anti-Rh titer of 1:80. The baby was greatly improved after the transfusion and made an uneventful recovery. The authors gave 2 other babies from Rh-negative mothers large transfusions of maternal blood this year with excellent results.

A study of 601 cord smears was made; 288 contained no normoblasts, while 34 contained more than 15. Among the 34 infants there were 5 deaths and 1 stillbirth. Five of the 6 mothers were Rh positive, and 1 was Rh negative. Of the 11 infants of Rh-negative mothers in the group of 34, 9 received a cord transfusion; 1 premature infant died.

The author believes that cord transfusions have a definite place in the treatment of prematurity and in combating shock in the infant following difficult deliveries, and may be useful in the anticipation of the development of erythroblastosis in infants of Rh-negative mothers or in the treatment when this is present at birth.

AUTHOR'S ABSTRACT.

ANTI RH AGGLUTININS IN THE MATERNAL BLOOD WITHOUT SYMPTOMS OF HEMOLYTIC ANEMIA IN THE NEWBORN INFANT. ALTON GOLDBLOOM and HERBERT LUBINSKI, J. Pediat. **28**:83 (Jan.) 1946.

The presence of anti-Rh agglutinins in the serum of a pregnant or parturient woman nearly always is followed by a more or less severe anemia in the newborn infant. Dockeray and Sachs have reported 4 cases in which, in spite of the presence of anti-Rh agglutinins in the maternal serum, the newborn infants did not exhibit clinical symptoms of hemolytic disease. However, in 2 of these cases it is doubtful that the antibodies were true anti-Rh agglutinins. The remaining 2 cases were not investigated sufficiently to exclude a slight anemia or jaundice.

Goldbloom and Lubinski observed the following case: A woman, delivered of her third child, was found to be Rh negative, while the husband and their three children were Rh positive. On the day of delivery anti-Rh agglutinins were found to be present in the woman's serum. Therefore the child was kept under close observation. However, the infant demonstrated no clinical or laboratory signs of hemolytic disease of the newborn. Red cell counts and hemoglobin estimations were done daily during the period of hospitalization.

The following explanation may be offered: Normal isoagglutinins pass through the placenta in 66 to 77 per cent of cases when blood groups are compatible. The same may hold true with regard to the anti-Rh agglutinins. On the other hand, unknown factors, which may be called "disposition," may be of importance for the course of the disease. This is demonstrated by a case in which identical Rh-positive twins, infants of an Rh-negative mother, reacted differently: One twin became severely ill, while the other showed hardly any clinical signs of disease.

AUTHORS' ABSTRACT.

ATELECTASIS OF THE NEWBORN: TREATMENT BY BRONCHOSCOPIC DRAINAGE. HOWARD P. HOUSE and HAROLD OWENS, J. Pediat. **28**:207 (Feb.) 1946.

This is a report on bronchoscopic aspiration as an adjunct in treatment of patients with severe congenital atelectasis due to obstruction of the bronchi with body secretions. Of 23 patients treated with the bronchoscope by the authors, 8 (34.7 per cent) died. Of the 8 deaths, postmortem examination revealed only 2 to be due to true atelectasis, leaving 2 deaths in 17 cases of true atelectasis, or 11.7 per cent.

Bronchoscopic aspiration is indicated in any case of atelectasis of the newborn due to bronchial obstruction which has failed to respond to the usual methods of conservative treatment. In most cases encountered the infants are premature. The clinical picture of atelectasis of the newborn secondary to bronchial obstruction is presented.

Careful examination of the infant, including roentgenologic examination, should be made to rule out various pathologic entities resembling congenital atelectasis due to bronchial obstruction, such as asphyxia, congenital disease of the heart and the blood vessels, congenitally cystic lung, cerebral trauma, dyscrasia of the blood, pulmonary infection, diaphragmatic hernia, congenital fetal atelectasis, etc.

After bronchoscopic aspiration there is usually progressive improvement in the child's respiration; complete relief most frequently occurs in six to eight hours after instrumentation. The procedure is completed in less than four minutes and seems to produce little, if any, shock and no secondary laryngeal edema.

The instrument used in the series was the new, improved, 3 mm. bronchoscope designed by Dr. Simon Jesberg, of Los Angeles, and described by him in the *Archives of Otolaryngology* (**33**:88, 1941).

AUTHORS' ABSTRACT.

DECREASE OF SERUM CHOLESTEROL ESTER IN HAEMOLYTIC DISEASE OF THE NEWBORN. ARNE ROTHEMEYER and EVELYN M. HICKMANS, Arch. Dis. Childhood **20**:160 (Dec.) 1945.

The serum cholesterol partition in 14 cases of hemolytic disease of the newborn was determined. The values for total cholesterol were within normal limits in all cases. Nine of the 14 patients showed a pronounced decrease or complete absence of the esterified fraction of cholesterol, findings similar to those demonstrated as characteristic of acute toxic hepatic injury.

KELLY, Milwaukee.

A CASE OF ERYTHROBLASTOSIS FOETALIS IN TWINS. FOURNIER, MENA BRITO and SALAS, Bol. méd. d. Hosp. Inf., México **3**:179 (July) 1945.

The mother had three pregnancies. From the first, there was a normal live infant. The second offspring died in utero. The offspring of the third pregnancy are the theme of this article. One of the twins was born dead. The father was Rh positive; the mother, her sisters and her mother were Rh negative; the live child was Rh positive and the other was Rh negative. The dead twin had hepatomegaly, splenomegaly and a high proportion of erythroblasts in the blood. In the live twin there was a moderate number of normoblasts in the blood.

According to the final clinical diagnosis there was erythroblastosis fetalis in the live twin and the stillborn twin was dead six days before birth. According to the pathologicoanatomic diagnosis the dead twin probably had erythroblastosis fetalis and the live child was probably normal.

It is interesting to note that there was no agreement between the clinician and the pathologist. In view of the findings of the latter, however, it may be accepted that the dead twin presented the picture, more or less complete, of erythroblastosis fetalis, while the live twin possibly did not exhibit the syndrome, or if it did, it was to a slight degree.

MADERO, México, D. F., Mexico.

COLOR PERCEPTION OF NEWBORN INFANTS. F. STIRNIMANN, Ann. pædiat. **163**:1 (July) 1944.

Experimentally, the author succeeded in proving that the newborn infant distinguishes the different colors. Contrast excites his feelings more intensively and

enables one to see that he responds differently to a circular surface than to a cross line. It also shows that the newborn infant perceives moving objects in the field of vision.

AUTHOR'S SUMMARY.

USE OF AKTEDRON IN NEWBORN. I. GAAL and J. KATONA, Ann. pædiat. **164**:150 (March) 1945.

The effect of the product Aktedron (l-phenyl-2-aminopropane hydrophosphate) in combating the difficulty of feeding sleepy newborn infants was investigated. The effect was convincing: The infants became lively and nursed with satisfaction. Unpleasant secondary effects were rare and of no importance. One can assume that the substance affects not alone the cerebral cortex and the medulla oblongata, but also the center in the hypothalamus.

AUTHORS' ABSTRACT.

Acute Contagious Diseases

PENICILLIN TREATMENT OF SCARLET FEVER: BACTERIOLOGIC STUDY OF THE NOSE AND THROAT OF PATIENTS TREATED INTRAMUSCULARLY OR BY SPRAY WITH PENICILLIN AND A COMPARISON WITH SULFADIAZINE. MANSON MEADS, M. EUGENE FLIPSE JR., MILDRED W. BARNES and MAXWELL FINLAND, J. A. M. A. **129**:785 (Nov. 17) 1945.

In a study of 36 patients with scarlet fever, 9 received no chemotherapy, 9 received full doses of penicillin intramuscularly for seven days, 9 received sulfadiazine orally in full dosage for seven days and 9 received penicillin locally as a nose and throat spray for seven days. Progress was followed by cultures of material from nose and throat.

Disappearance of the streptococci within forty-eight hours was noted in the second group with failure of the original type of streptococci to reappear when therapy was continued for the seven days. Sulfadiazine suppressed the number of streptococci for the period of treatment only. Local application of penicillin had little effect on pharyngeal cultures but did keep the nose free of streptococci for the period of treatment.

BAIRD, Wauwatosa, Wis.

THE USE OF TRACHEOTOMY IN BULBAR POLIOMYELITIS. DANIEL F. GLASER, J. Pediat. **27**:560 (Dec.) 1945.

Bulbar poliomyelitis is that form of the disease in which the infection involves the brain stem and gives rise to clinical impairment of any of the cranial nerves. The prognosis becomes grave when the hypoglossal, pharyngeal and vagus nuclei are involved.

The causes of death from central paralysis include failure of the respiratory center and cardiovascular collapse. Because of the inability to swallow, the nasal and buccal secretions form a "puddle" in the posterior part of the pharynx. Aspiration pneumonia and atelectasis frequently result. Postural drainage and tracheotomy aid in removing and in by-passing this puddle.

Because of the accumulated secretions in the posterior part of the pharynx, aspiration pneumonia and atelectasis are almost certain to follow should the patient be placed in a respirator. However, by attachment of an oxygen supply directly to a tracheotomy tube a valve mechanism is set up. There is positive pressure in the oxygen supply line which makes exhaling through it impossible. The exhaled gases tend to escape around the tracheotomy tube and out through the nasopharynx. This tends to force the accumulated secretions out where they may be removed by suction. During inspiration the supply tends to be derived from the oxygen supply, and consequently the "puddle" of secretions is by-passed. For direct connection of the oxygen supply to the tracheotomy tube, the tube was altered by soldering a nipple to the inside tube.

Two patients with failure of the respiratory center due to bulbar poliomyelitis were treated with the valve. The first patient was removed from the respirator

after eleven days. After six months there is still some degree of residual paralysis, but the patient is otherwise in good health. The second patient died on the eighth hospital day of cardiovascular collapse.

From August to December, 1944, 8 patients with severe bulbar poliomyelitis were seen. Of these the only one to survive was the first patient mentioned, who was removed from the respirator after eleven days.

AUTHOR'S ABSTRACT.

MENINGOCOCCIC MENINGITIS. C. C. ROTONDE and N. I. HANDELMAN, J. Pediat. **27**:576 (Dec.) 1945.

Multiple cases of meningococcic meningitis in the same family are known to be infrequent. During the epidemic in Louisville, Ky., in the winter of 1943 and 1944, 3 infants of the same family with meningococcic meningitis were admitted to the isolation ward of the Louisville General Hospital within a period of thirty-six hours. The first patient was an 11 month old Negro girl, one of twins, with onset of symptoms less than twenty-four hours prior to admission. By means of a lumbar puncture the diagnosis was confirmed. The child died shortly after onset of therapy. Postmortem examination showed meningococcic meningitis. The patient's twin sister and a 2 year old sister were subsequently admitted with the typical history and physical and laboratory evidence of meningococcic meningitis. They both made uneventful recoveries with chemotherapy.

AUTHORS' ABSTRACT.

GENERALIZED VACCINIA AND PROBABLE INDUCED THIAMINE DEFICIENCY IN A CONGENITALLY HYPOTHYROID CHILD. EASTON M. GROPPER, CARL LAMANNA and CHESTER A. STEWART, J. Pediat. **27**:595 (Dec.) 1945.

An example of generalized vaccinia in a congenitally hypothyroid child is reported.

A virus was isolated from one of the patient's lesions. Experiment on animals revealed the immunizing properties of this virus to be identical with those of vaccinia virus.

The administration of thiamine chloride promptly relieved pronounced irritability attributed to thiamine deficiency induced by overdosage with desiccated thyroid.

The administration of B complex vitamins had no appreciable effect on recurrent attacks of mild fever which accompanied thyroid therapy. These supplementary vitamins and a voracious appetite also failed to prevent loss of weight during the first four months of thyroid therapy.

AUTHOR'S ABSTRACT.

EPIDEMIC POLIOMYELITIS. LOUIS P. GEBHARDT and WILLIAM M. MCKAY, J. Pediat. **28**:1 (Jan.) 1946.

Epidemiologic studies of the epidemic of poliomyelitis in Utah, in 1943, at which time 400 cases were reported, revealed that infection by direct contact could be traced in only 13.6 per cent of 241 cases of the disease surveyed. Water supplies, milk supplies and swimming pools failed to reveal the means by which the disease was spread. Fresh unwashed or unpeeled fruits and vegetables were eaten five to fourteen or more days previous to the development of the disease in 206 out of 206 cases surveyed. Moreover, the peak seasons for fresh fruit and vegetables correlated with the greatest incidence of cases of poliomyelitis in three states surveyed: Utah, New York and California.

Twenty families with multiple cases (totaling 45) were surveyed. In each of six of the twenty families 2 children contracted the disease on the same day. In nine other families there was an interval of five days or less. This suggests infection at the same time from the same source.

The incidence and increase of flies correlated with the incidence as well as with the increase in the number of cases of poliomyelitis, September being the

peak month for both. Flies have been shown by many investigators to carry the virus of poliomyelitis.

Where there were poorly developed sewage units there was a high incidence of poliomyelitis, and in one area of faulty sewage disposal the morbidity rate was 468, compared with the state morbidity rate of 61.5.

Closing of public schools during the peak month of September failed to affect the rise of the epidemic trend in the school age groups of 6 to 17. The tendency in the state for cases in this same age group to decline in number was not affected when school was reopened on September 29. About 31,000 students were studied in this school age group.

It is suggested from these studies that poliomyelitis is a disease of the "filth-borne type" and that infection is probably accidental, resulting from the eating of contaminated food, such as fresh fruits and vegetables. It is suggested that flies may transmit the virus from sewage to fresh foods.

AUTHORS' ABSTRACT.

RESISTANCE OF COTTON RATS TO THE VIRUS OF POLIOMYELITIS: AS AFFECTED BY INTAKE OF VITAMIN A, PARTIAL INANITION AND SEX. H. M. WEAVER, with the technical assistance of ROSE FUCINARI and NORMA HASTINGS, J. Pediat. **28**:14 (Jan.) 1946.

This article records the results of twelve experiments which were designed to test the effects of diets deficient in vitamin A, of partial inanition and of sex on the susceptibility and on certain immunologic responses of cotton rats to the virus of poliomyelitis.

Suspensions of the Armstrong-Lansing strain of the virus of poliomyelitis were injected or instilled in varying quantities into the cerebrum, stomach, colon, peritoneal cavity, external nares and blood stream and beneath the skin of the back and beneath the pharyngeal mucosa. In addition, the animals of one experimental group were allowed to remain in intimate contact with cotton rats succumbing to the effects of intracerebral inoculations with the virus. Finally, each cotton rat of still another experimental group was fed the brain stem and spinal cord freshly removed from a cotton rat paralyzed with poliomyelitis.

Each of the cotton rats which failed to show paralysis after an experimental inoculation with the virus was subjected to three way reinoculations with the virus at intervals of twenty-five days.

The results of these experiments yield no evidence to indicate that diets deficient in vitamin A affect the susceptibility or the resistance of cotton rats to the virus of poliomyelitis when the latter is administered by injections into the cerebrum, by instillations into the bronchii, by feeding an infected brain stem and spinal cord or by contact with an infected cotton rat.

Evidence was presented to indicate that cotton rats fed diets deficient in vitamin A are more susceptible to the virus of poliomyelitis than are controls when the virus is administered by intratonsillar injections, by intracolonic instillations, by intraperitoneal injections, by intranasal instillations, by subcutaneous injections and by intracardiac injections.

Some evidence was presented to indicate that in cotton rats fed diets deficient in vitamin A the mucosa of certain parts of the alimentary tract may become more permeable to the virus of poliomyelitis than is the case among the controls.

It would appear that sex and the partial inanition suffered by all rats fed the diet deficient in vitamin A played no primary part in the results obtained in this study.

AUTHORS' SUMMARY.

RUBELLA DURING PREGNANCY OF THE MOTHER, WITH ITS SEQUELAE OF CONGENITAL DEFECTS IN THE CHILD. N. MCALISTER GREGG, M. J. Australia **1**:313 (March 31) 1945.

Gregg reviews his own work and the medical literature on congenital defects in infants following maternal rubella.

GONCE, Madison, Wis.

PROPHYLAXIS AGAINST MEASLES. F. GOMEZ, Bol. méd. d. Hosp. inf., México **1**: 37 (March) 1944.

The author describes how a case of measles appeared in the babies' ward. Since the diagnosis was not made until the classical symptoms had appeared, the conditions for infecting the whole ward were almost perfect.

Not earlier than the third day of the exposure some children began receiving injections of adult's serum, and others, of blood; the first group received three injections five days apart in a total amount of 30 to 40 cc. The other group received blood intravenously, the dose being no less than 50 cc. every five days. Still another group received both serum and blood. Some children left the hospital after the second injection, but of these only 1 contracted abortive measles. None of the rest caught the disease.

MADERO, México, D. F., Mexico.

A CASE OF PROSTATITIS ACUTA ACCOMPANYING MUMPS. W. J. VAN DER HOOFT, Nederl. tijdschr. v. geneesk. **86**:563 (March 7) 1942.

The author reports on a case of acute prostatitis accompanying mumps in a boy aged 16 years.

VAN CREVELD, Amsterdam, Netherlands.

Acute Infectious Diseases

THE PREVENTION OF RHEUMATIC RECURRENCES IN CHILDREN BY THE USE OF SULFATHIAZOLE AND SULFADIAZINE. R. E. WOLF, L. W. RAUH and R. A. LYON, J. Pediat. **27**:516 (Dec.) 1945.

Small doses of sulfathiazole and sulfadiazine were administered daily to a group of children over a period of one or two years to prevent respiratory infections which in turn might lead to the recurrence of rheumatic fever. The dosage of sulfathiazole was 0.5 Gm. twice a day and of sulfadiazine 0.5 Gm. once a day. The drug was administered to children who were being observed in a convalescent home, in a special school and in an outpatient clinic. A total number of 78 children treated for eighty-one patient seasons made up the group, and none of these patients experienced any recurrences of rheumatic fever during the period of treatment. One child of the group had a recurrence of the disease about three months after the termination of the course of treatment, and 2 had bacterial endocarditis, which responded favorably to penicillin therapy.

Reaction to the sulfathiazole consisted chiefly of leukopenia, while the reaction to sulfadiazine consisted chiefly of the presence of albumin in the urine without other symptoms of nephritis. A total number of fifteen reactions occurred during ninety patient seasons, and all these reactions were mild. It was the conclusion that these two drugs were safe to administer for a long period of time and that they were effective in reducing the chances of recurrence of rheumatic fever. However, whenever the drugs were administered it seemed wise to keep the child under close observation to be sure that he took the drug regularly and also to watch for the early signs of the development of complications. If the patient was cooperative and it was possible to perform laboratory tests such as white blood cell counts and urinalyses at regular intervals, the drug could be given in the outpatient dispensary or in the physician's office without danger.

AUTHORS' ABSTRACT.

EXPERIMENTAL INTESTINAL MYIASIS IN MAN. MICHAEL KENNEY, Proc. Soc. Exper. Biol. & Med. **60**:235 (Nov.) 1945.

Large gelatin capsules containing 20 dipterous larvae of a single species (Musca domestica, Calliphora and Sarcophaga) were given with two glasses of water on a fasting stomach to 60 human volunteers in the Belgian Congo. In 50 instances gastrointestinal disturbances, varying combinations of vomiting, diarrhea and abdominal distress developed but subsided within a few hours to forty-eight hours after elimination of the larvae from the intestine. Repeated study of the stools

examined routinely, in some instances for twelve months, revealed no evidence of larvae. The author believes on the basis of these experiments that swallowing living maggots does not produce true intestinal myiasis in man.

HANSEN, Galveston, Tex.

MYELITIS FROM ANTIRABIC VACCINE. FERNANDO LÓPEZ CLARES, Bol. méd. d. Hosp. inf., México **1**:23 (May-June) 1944.

L. N. A., a 2 year old girl, was admitted to the hospital three weeks after she had been bitten by a rabid dog. The complaint was that after the seventh antirabic injection her temperature rose to 39 C. (102.2 F.) and she experienced pharyngitis and constipation. The treatment was discontinued. Six days later her lower right limb, the fingers of both hands and her bladder and rectum were paralyzed.

On her admission, there were enough symptoms and signs to support the diagnosis of myelitis from antirabic vaccine.

The child's recovery was slow but uneventful, and she was discharged four months later completely cured.

It is interesting to note that in the last thirteen years there have been 10 cases of this type of paralysis in 50,000 treatments, and of those 10 cases, only 2 were in children.

MADERO, México, D. F., Mexico.

TYPHOID AND TYPHOID MENINGITIS IN AN INFANT. PEDRO DANIEL MARITÍNEZ, Bol. méd. d. Hosp. inf., México **1**:57 (May-June) 1944.

F. L. A., an 18 month old boy, was admitted to the hospital in a comatose state. His illness had begun two weeks previously with diarrhea and vomiting; one week later there had been fever and convulsions, and four days before his admission there had been somnolence, trismus, internal strabismus of the left eye and constipation. Artificial feeding had been begun a month before his admission.

Germs of the typhoid group were cultured from the spinal fluid. Other tests and clinical examinations were also positive in result. The roentgenologic studies revealed bronchopneumonia of the upper lobe of the left lung.

The child did not respond to treatment, and died thirty-two hours later.

MADERO, México, D. F., Mexico.

Chronic Infectious Diseases

CYSTIC TUBERCULOSIS OF THE BONE IN A CASE OF MILIARY TUBERCULOSIS. RUSSELL J. BLATTNER and CHIEH SUNG, J. Pediat. **27**:579 (Dec.) 1945.

Cystic tuberculosis of the metaphysis and epiphysis of the tibia is described in a 2 year old child with miliary tuberculosis. The roentgenologic appearance of the osseous lesion was unusual, being cystic on anteroposterior view and punched out on lateral view. Antemortem diagnosis was made by demonstration of tubercle bacilli on direct smear of material aspirated from the bone. Inoculation of this aspirated material into two guinea pigs produced tuberculosis.

AUTHORS' ABSTRACT.

COMPARISON OF THE GOLDEN HAMSTER TO THE GUINEA PIG FOLLOWING INOCULATIONS OF VIRULENT TUBERCLE BACILLI. W. STEENKEN JR. and PHILIP F. WAGLEY, Proc. Soc. Exper. Biol. & Med. **60**:255 (Nov.) 1945.

Virulent strains of tubercle bacilli were injected into golden hamsters (Cricetus auratus) and guinea pigs (20 in each group) and the degree of macroscopic tuberculosis and of reaction to cutaneous tests with old tuberculin was determined. It was found that hamsters are highly resistant to doses of virulent strains of human type of tubercle bacilli, in contrast to guinea pigs, among whom widespread tuberculosis developed. The authors conclude that hamsters are of little or no value in routine diagnosis of tuberculosis.

HANSEN, Galveston, Texas.

RETROGRADE LYMPHATIC INFECTION IN CHILDHOOD TUBERCULOSIS: GENERAL CONSIDERATIONS. ARTURO SCROGGIE, Arch. Hosp. d. Niños Roberto del Rio **13**:43 (June) 1945.

The author points out in this article the methods by which tuberculosis of the lymph nodes of the mediastinum or other locations can produce stasis of lymph. Then, by retrograde flow of toxic and infectious products, various manifestations of primary tuberculosis are produced. Particularly well presented is the matter of pleurisy, which Dr. Scroggie feels can be allergic and due to the reflux of allergenic products of the infecting organism, or which is sometimes infectious because of lymphatic reflux of the tubercle bacillus itself.

MILLER, Newark, Ohio.

CONTRIBUTIONS TO THE RADIOLOGIC STUDY OF THE PROPAGATION OF TUBERCULOSIS BY THE RETROGRADE LYMPHATIC PATH. MANUEL SALGADO, Arch. Hosp. d. Niños Roberto del Rio **13**:69 (June) 1945.

This is a series of roentgenologic studies of calcification of mediastinal lymph nodes. In this series, the author points out that the nodes seem to be calcified in groups corresponding to the anatomic lymph flow. In a few cases he presents serial studies to demonstrate progression of calcification backward along the lymphatic channels.

MILLER, Newark, Ohio.

GENERALIZED ACTINOMYCOSIS WITH PRIMITIVE PULMONARY AND CARDIAC FOCI AND MULTIPLE METASTATIC CUTANEOUS MANIFESTATIONS. ANTONIO DUBÓN A., Bol. méd. d. Hosp. inf., México **1**:1 (May-June) 1944.

C. V. M. was a 13 year old girl. Ten months before her admission to the hospital the disease began, being characterized by pain in the lower lobe of the right lung and other pulmonary symptoms; later the cardiac symptoms appeared, and there was also general malaise. Two months afterward the tumors began to appear, first on the back of the right hand and later, with intervals of between ten and fifteen days, on the rest of the body. The tumors were about 7 cm. in diameter, hard, nonpainful and cyanotic. In a few days there was sloughing in the center with thick oily pus; there were also many small round granulations resembling sulfur dust.

The laboratory and the roentgenologic observations and, later, the observations of the department of pathology helped to clear the diagnosis of this rare disease.

MADERO, México, D. F., Mexico.

GENERALIZED TUBERCULOSIS IN A CHILD TWO YEARS OF AGE. MAXIMILIANO SALAS, Bol. méd. d. Hosp. Inf., México **1**:13 (May-June) 1944.

This patient was first admitted to the hospital about a year ago, complaining of fever, frequent paroxysms of cough, asphyxia and restlessness. Since then the child has been admitted several times with similar symptoms. On one occasion the diagnosis of bilateral bronchopneumonia was made.

About four months after the first admission the patient was brought in critically ill, but in spite of the therapy he died a few hours later.

The department of pathology found generalized tuberculosis with typical lesions in the lungs, liver, spleen and thoracic and abdominal glands.

It must be stated that the clinician had not had sufficient grounds even to suspect the true diagnosis.

MADERO, México, D. F., Mexico.

TUBERCULOID LEPROSY. E. ESCALONA, Bol. méd. d. Hosp. inf., México **1**:43 (March) 1944.

L. H. G., a 13 year old girl, was admitted to the hospital with the diagnosis of erythema multiforme.

The dermatologist found that the cutaneous lesions exhibited certain peculiarities of location, form and structure. Also it was found that the lesions were disesthetic.

These data, together with the presence of neuritis and amyotrophia, were the bases for the diagnosis of tuberculoid leprosy. Both the laboratory tests and the pathologic examinations helped to support the diagnosis.

MADERO, México, D. F., Mexico.

RICKETS AND CONGENITAL SYPHILIS. ALVAREZ DE LOS COBOS, Bol. méd. d. Hosp. inf., México **1**:46 (May-June) 1944.

S. V., a 20 month old boy, was admitted to the babies' ward because of sweating of the head, pain in the muscles when moved, bending and distortion of the legs and wasting.

At the physical examination, it was found that the fontanel was wide open and there were craniotabes, rachitic rosary and Harrison's groove. The roentgenologic studies indicated both rickets and syphilis. The chemical composition of the blood and the serologic reactions supported the diagnosis also.

The patient improved under proper treatment.

MADERO, México, D. F., Mexico.

Diseases of the Blood, Heart and Blood Vessels and Spleen

TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN: REPORT OF CASES TREATED WITHOUT ANTI-COAGULANT AGENTS. JESSAMINE R. GOERNER, ARTHUR J. GEIGER and FRANCIS G. BLAKE, Ann. Int. Med. **23**:491 (Oct.) 1945.

The authors had previously used penicillin in small doses for short courses with unsuccessful results. After this experience they adopted massive dose therapy, giving 240,000 units of penicillin daily for a period of three to four weeks.

The penicillin was given by continuous intravenous infusion, the daily quantity of penicillin being dissolved in 1,500 cc. of isotonic solution of sodium chloride or 5 per cent solution of dextrose.

Twelve patients were treated by this method; 11 of these are alive and well. In several instances a year has elapsed since termination of therapy.

READING, Galveston, Texas.

HORSE BRAIN THROMBOPLASTIN: II. EFFECT OF VARIOUS FACTORS ON ACTIVITY OF HORSE BRAIN EXTRACTS. LOUIS A. KAZAL, AEME HIGASHI and L. EARLE ARNOW, Proc. Soc. Exper. Biol. & Med. **60**:196 (Nov.) 1945.

The authors describe a method for preparation of large quantities of thromboplastin from horse brain; they studied the material in relation to its use in the quantitative determination of prothrombin by the one stage method. The optimal mixture of acetone-desiccated horse brain powder was a 6 per cent suspension in 0.85 per cent solution of sodium chloride. The optimal temperature for preparation was 50 C. for fifteen to thirty minutes. Exposure to temperature between 50 C. and 100 C. resulted in partial destruction of thromboplastic activity. It would appear that the use of horse brain as a source of thromboplastin would have practical advantages.

HANSEN, Galveston, Texas.

A CASE OF CHRONIC IDIOPATHIC THROMBOPENIC PURPURA WITH SPLENOCTOMY. R. SOTO A., Bol. méd. d. Hosp. inf., México **1**:11 (March) 1944.

The author presents a girl 12 years of age, whose chief complaint was the appearance, four years previously, of punctate hemorrhage in different parts of the body without any evident cause; also, intense ecchymosis with the slightest traumatism. The things of interest in the blood pictures are the increased bleeding time, the normal coagulation time and the decreased platelet count. These data, together with the myelocyte count, speak for thrombopenic purpura.

The injection of rattlesnake venom produced no results. The child was then splenectomized. For three months she remained free of purpuric manifestations, but since then she has had them anew. For this reason, her thrombopenia is called idiopathic. The author believes that there is a possibility of aberrant spleens.

MADERO, México, D. F., Mexico.

A CASE OF THROMBOPENIC PURPURA. J. MUÑOZ TURNBULL, Bol. méd. d. Hosp. inf., México **1**:17 (March) 1944.

The author presents the history of a boy 3 years and 7 months of age who became ill three days before he was admitted to the hospital with profuse rhinorrhagia, which was not checked by the usual methods. There were also large purpuric spots over the entire surface of the body. Once the patient was in the ward, an anterior and posterior nasal packing was done which did not entirely check the hemorrhage. Transfusions were begun and continued daily. The patient had a temperature between 39 and 40 C. (102.2 and 104 F.) that lasted five days and subsided with the removal of the packing. There were an increased bleeding time, a normal coagulation time and a low platelet count. The myelocyte count was typical of thrombopenic purpura.

The patient remained in the hospital almost a month, being discharged apparently cured. Five months later the social service reported that the child was still in good health.

MADERO, México, D. F., Mexico.

NONTHROMBOPENIC PURPURA. ANTONIO PRADO VÉRTIZ, Bol. méd. d. Hosp. inf., México **1**:28 (May-June) 1944.

A 12 year old boy began to be ill a month previous to his admission to the hospital, complaining of arthralgia of the knees, elbows and wrists. One week later there were petechiae on the limbs and hypogastrium. Three days before his admission he had epigastralgia and vomiting. There never was any fever. On his admission the child was found to have chronically infected cryptic tonsils, dental caries of the fourth degree, petechial spots on the limbs, arthralgia and bloody urine.

The patient had a previous history of spasmophilia, urticaria and amygdalitis. There was no history of rheumatism or chronic intoxication.

The laboratory tests helped to confirm the diagnosis of acute hemorrhagic glomerulonephritis and purpura of the anaphylactoid or Schönlein-Henoch type.

The patient was discharged, completely cured, three months later, after his caries had been treated and his tonsils removed, and after he had been desensitized with progressive doses of histamine.

MADERO, México, D. F., Mexico.

A CASE OF PAROXYSMAL VENTRICULAR TACHYCARDIA. J. D. LEBRET and A. D. ERKELENS, Maandschr. v. kindergeneesk. **11**:110 (Jan.) 1942.

A case of paroxysmal ventricular tachycardia resulting from an infection, in a boy 8 years old, is described. The child died of sudden heart failure. The treatment had chiefly consisted in administrating quinidine. A typical electrocardiogram is shown.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF TACHYCARDIA IN A YOUNG CHILD. N. HAVERKAMP BEGEMANN, Maandschr. v. kindergeneesk. **11**:122 (Jan.) 1942.

A case is reported of auricular flutter in a girl 2½ years old, who presented symptoms of congenital heart disease. The direct cause of the tachycardia probably was myocarditis.

VAN CREVELD, Amsterdam, Netherlands.

LYMPHOSARCOLEUKEMIA. C. HOOFT and H. COMPERNOLLE, Maandschr. v. kindergeneesk. **11**:191 (April) 1942.

A boy 5 years old showed a tumor in the epigastric region which could be diagnosed as a tumor originating from the liver. At the time of his entrance into the hospital neither blood nor bone marrow showed pathologic changes, except that 3 per cent of the bone marrow cells were abnormal and probably paramyeloblasts. One month later the bone marrow at different places appeared to be totally infiltrated with one type of cells, namely small round cells, somewhat larger than a lymphocyte with round nucleus with uniform chromatin spots and a distinct blue layer of protoplasm containing small vacuoles. The same pathologic cells were present in the blood (3 per cent) and in the ascites fluid. The results of the autopsy and of the investigation of blood and bone marrow seemed to justify the diagnosis of lymphosarcoleukemia (Isaacs).

VAN CREVELD, Amsterdam, Netherlands.

I. THE DETERMINATION OF THE AMOUNT OF CARBOMETHEMOGLOBIN AND SULFHEMOGLOBIN IN SMALL QUANTITIES OF BLOOD. J. H. P. JONXIS, Maandschr. v. kindergeneesk. **11**:204 (April) 1942; II. ON THE OCCURRENCE OF CARBOMETHEMOGLOBIN AND SULFHEMOGLOBIN IN CHILDREN, ibid. **12**:143 (Feb.) 1943.

In the first article the author describes a colorimetric method for the determination of the percentages of derivatives of hemoglobin, carbomethemoglobin and sulfhemoglobin, in small quantities of blood. The method is based on the differences in absorption of light of certain wavelengths shown by these derivatives of hemoglobin.

In the second article he discusses some results obtained by this method in some clinical cases. The theory of Kallner (1942) that cyanosis after administration of sulfanilamide may be caused by the formation of a combination of sulfanilamide and hemoglobin is probably not right.

VAN CREVELD, Amsterdam, Netherlands.

ON SO-CALLED SPONTANEOUS HYPOGLYCEMIA IN CHILDHOOD. J. C. SCHIPPERS, Maandschr. v. kindergeneesk. **11**:271 (June) 1942.

Schippers reports two observations of attacks of spontaneous recurrent hypoglycemia in young children. The author tries to find the explanation in disturbances in coordination, which in themselves should be caused by retarded development of the regulation of the carbohydrate metabolism. Further, the condition was observed in an adult, which makes it probable that this syndrome may also occur as a familial disease.

VAN CREVELD, Amsterdam, Netherlands.

FAMILIAL HEREDITARY HEMOLYTIC JAUNDICE IN EARLY CHILDHOOD. C. HOOFT and L. VERHOESTRAETE, Maandschr. v. kindergeneesk. **11**:417 (Aug.) 1941.

The authors report on 2 cases of familial hereditary hemolytic icterus in 2 young sisters. After an extensive examination it was decided that several members of the paternal family suffered from compensated or latent forms of the disease. When the patient is a young child due attention should be paid to the differential diagnosis of this disease with a number of other erythronoclastic diseases. In another case which could be followed from birth until the patient was 2 years old the gradual rise of different symptoms of decomposition could be observed. In the infant and in the young child the symptoms differ from the classical symptoms in adults. The symptoms of decomposition in the erythropoietic system and in relation to these, the osseous abnormalities, also, are more pronounced. However, the symptoms of decomposition of the liver are less distinct in the beginning. The value of the extirpation of the spleen and of therapy by means of transfusions are discussed.

VAN CREVELD, Amsterdam, Netherlands.

VALUE OF THE SYMPTOMS OF THE PERSISTENT BOTALLO DUCT FOR THE DETERMINATION OF THE SIZE OF THE SHUNT. W. C. AALSMEER, Maandschr. v. kindergeneesk. **12**:271 (July) 1943.

The physical signs of persistence of the ductus arteriosus are best arranged in two classes, those found on the venous side and those located in the arterial system. The extent of the arterial syndrome is the most reliable index of the magnitude of the shunt. If the arterial syndrome is less pronounced than expected one should first think of cardiac insufficiency; also the possibility of a complicating infantile stenosis of the aortic isthmus should be considered. Attention is drawn to a new sign in cases of patent ductus arteriosus, a local increase of the vascular syndrome observed when the limb in question is placed vertically.

VAN CREVELD, Amsterdam, Netherlands.

INCIDENCE OF COLOR-BLIND BLEEDERS IN FAMILIES: ITS SIGNIFICANCE WITH RESPECT TO CYTOLOGIC SYMPTOMS OF HEREDITY IN MEN. P. J. WAARDENBURG, Nederl. tijdschr. v. geneesk. **86**:1880 (July 25) 1942.

Including a Dutch case the author gives a review of the literature on the coincidence of hemophilia and colorblindness in the same person among different members of one family. He discusses critically the evidences for chromosomal linkage, crossing over and mutation, and stresses the necessity of procuring diagnostic data by means of Nagel's anomaloscope and of investigating the direct and collateral ancestors in every possible direction. As to sex-chromosome-linked characters, the abnormal types in siblings appear to surpass the normal in frequency, though, theoretically, this would not be expected.

VAN CREVELD, Amsterdam, Netherlands.

CHLOROMA AND THE CAUSE OF ITS GREEN COLOR. J. ZELDENRUST, W. L. C. VEER and J. H. W. NOTA, Nederl. tijdschr. v. geneesk. **87**:875 (May 8) 1943.

A case is reported of myeloid chloroleukemia in a boy aged 3½ years. In agreement with Thomas it was found that the green color of the growths on the periosteum of the bones of the face and the skull is due to protoporphyrin.

VAN CREVELD, Amsterdam, Netherlands.

INFLUENCE OF VITAMIN C ON THE BLOOD PICTURE OF PATIENTS WITH LEUKEMIA. C. L. C. VAN NIEUWENHUIZEN, Nederl. tijdschr. v. geneesk. **87**:896 (May 8) 1943.

After a short discussion of the available methods of treatment of chronic leukemia, their indication and contraindication, a report is given on the influence of intravenous injections of ascorbic acid (500 mg. per injection) on the number of and on the relationship between different forms of white cells in a patient with myeloid leukemia. The number of leukocytes decreased from 235,000 to 67,500, with a temporary increase (relative and absolute) of the number of lymphocytes and a slight eosinophilia. The immature forms were not reduced, in contrast to what was observed during roentgenologic treatment. The concentration of hemoglobin and the number of erythrocytes increased and the bone marrow showed increased erythropoiesis. For some months the patient's condition was subjectively greatly ameliorated.

In a woman of 30 with lymphatic leukemia a transitory decrease of lymphocytes from 480,000 to 368,000 was observed, but there was no subjective amelioration of the condition during the treatment with injections of ascorbic acid. One treatment of the spleen with roentgen rays caused the lymphocytes to decrease from 500,000 to 14,000.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Lungs, Pleura and Mediastinum

TUMOR OF THE MEDIASTINUM. A. TORRES DE ANDA, Bol. méd. d. Hosp. inf., México **1**:54 (March) 1944.

F. D., a 14 year old boy, admitted to the hospital for an intercurrent disease, on examination was found to have a tumor of the posterior mediastinum, which was probably of nervous origin.

The child was operated on uneventfully and was discharged twenty-eight days later, completely cured.

The department of pathology confirmed the clinical diagnosis, saying that the tumor was a ganglioneuroma.

MADERO, México, D. F., Mexico.

PULMONARY ABSCESS AND ATELECTASIS FROM FOREIGN BODY. J. G. PAGOLA, Bol. méd. d. Hosp. inf., México **1**:59 (May-June) 1944.

E. R. V., a 7 year old boy, became ill seven months before admission. The complaint was that after he had swallowed a watermelon seed there was asphyxia and cyanosis which lasted fifteen minutes. For several days afterward there was a sensation of discomfort, and the patient began to cough and to have a slight but continuous fever.

At the examination, a slight flattening of the left side of the chest was noted, with diminished respiratory sounds, slight dulness and scattered rales.

Roentgenograms showed an infiltration of the base of the left lung.

By bronchoscopy a large amount of purulent secretion was found and aspirated. The seed was also removed. With this, the picture cleared up completely.

MADERO, México, D. F., Mexico.

ABSCESS OF THE LUNGS? R. POUS ROCA, Bol. méd. d. Hosp. inf., México **1**:71 (March) 1944.

Z. D. E., a 4 year old boy, was admitted to the observation ward with a tentative diagnosis of colibacillosis and pertussis, but the laboratory tests did not furnish any data to support that diagnosis.

The patient was treated with transfusions, dextrose solution by intravenous drip and vitamins. A few days later the patient coughed up a great deal of greenish phlegm tinged with blood. On this account, some new roentgenograms were taken which revealed the presence of an abscess in the lower lobe of the right lung. Sulfadiazine was then administered, and the patient began to improve slowly.

The differential diagnosis with pulmonary emphysema was never cleared, since the child improved with the therapy instituted.

MADERO, México, D. F., Mexico.

PNEUMOCYSTIS AS PARASITE IN MAN. G. VAN DER MEER, and S. L. BRUG, Nederl. tijdschr. v. geneesk. **86**:2066 (Aug. 15) 1942.

In smears of material from the lungs of a child who had died at the age of 3 months, Pneumocystis organisms were found in considerable numbers, not differing morphologically from Pneumocystis carinii as found in many animal species. Besides the classical cysts there were particular structures which the authors consider to belong to the life cycle of the parasite: 1. In the smears groups of nuclei were present, each with a more or less ill defined protoplasm, the whole, often together with a number of cysts, embedded in a pale rose matrix. 2. Corresponding to these groups honeycomb-like structures were found in sections of the lungs, each cell of the structures containing a small mass of protoplasm with a minute nucleus. Similar structures often were found in rats and mice infected with Pneumocystis organisms. Intracellular stages were absent, in man as well as in animals. Pneumocystis can hardly be considered a Coccidium.

CREVELD, Amsterdam, Netherlands.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

PROCTOLOGIC PROBLEMS OF THE PEDIATRICIAN. EDWIN F. PATTON, J. Pediat. **27**:532 (Dec.) 1945.

Incomplete fusion of the proctodeum and hindgut during late fetal life results in rectal obstruction, either by a partial diaphragm of epithelial tissue across the opening or by a ring of fibrous tissue around the opening. Colic, distention or bleeding as a result may be relieved by dilation, a small gloved finger serving well as the dilating instrument.

Fissure of the rectum or proctitis may be originated by passing a sharp object, a fiber or hard stools. A large otoscopic speculum with proper illumination makes a good examining instrument for determining these conditions, which cause pain on defecation and consequent voluntary retention. This vicious cycle of pain producing retention and retention producing hard stools, which cause pain and injury, must be relieved by allaying the pain and by producing regular, soft stools. Tetracaine hydrochloride or other local anesthetic applied before time for defecation eliminates most of the pain and thereby the fear of having a movement.

To establish a permanent habit there should be two regular times each day for defecation (best after breakfast and supper) which are never missed (there may be other times also if the urge develops). There should be an unhurried conscientious effort for ten to twenty minutes. If there has been no bowel movement by bedtime one should be secured by means of suppository or enema. The child should never be allowed to retire without having had a bowel movement during the day. One quart (950 cc.) of water should be drunk each day. Generous portions of stewed fruit (figs, prunes and apricots are best) should be served at breakfast and supper, and some dried fruits to be chewed between meals should be provided. Two generous portions of fibrous vegetables should be served daily. Bran or yeast may be used as desired.

Proprietary compounds of light liquid petrolatum (without magnesium oxide, cascara or phenolphthalein, unless ordered), 1 teaspoon to 1 ounce (4 cc. to 30 cc.) morning and evening, may be used as temporary aids. As the habit develops the size of the dosage may be gradually decreased, but administration should be twice a day, as before, until there is no further need.

Fissures may be coagulated with pure silver nitrate once or more, and if proctitis is obstinate, it may be treated topically in identical fashion. This program may have to be followed for weeks or months, treatment being tapered off as improvement takes place.

Rectal bleeding may be local, especially if the blood is fresh and red and streaks the outside of the stool rather than mixing intimately with it. All rectal bleeding should be studied for local source such as polyp, fissure, proctitis or ulcer, before there is investigation higher up.

Local perirectal irritation produced by fungus, pinworms, scabies or bacterial cryptitis may draw attention to this region by itching, by frequent small stools, or by resistance to defecation.

Rectal prolapse will usually cure itself in time if the prolapsed segment is merely replaced, and the stools kept soft, but if it does not improve in a reasonable time, submucous injections of a sclerosing agent by a proctologist are indicated.

Megacolon is sometimes favorably influenced by systematic dilations of a relatively narrow rectal sphincter.

A neuropathic lower colon fails to empty normally, stretches and becomes atonic. The resulting annoying and difficult type of constipation calls for faithfully securing regular evacuations by any or all of the means mentioned which are effectual, even including fairly frequent enemas.

AUTHOR'S ABSTRACT.

ACUTE GASTRIC ULCER WITH PERFORATION IN ONE OF PREMATURE TWINS. ALBERT A. ROSENBERG and MARY H. HEATH, J. Pediat. **28**:93 (Jan.) 1946.

A case is reported concerning one of homologous twins born at eight months' gestation, weighing 3 pounds 10 ounces (1,590.3 Gm.). Both infants did well until

the ninth day, when this infant became listless and vomited. From this time on vomiting was frequent, and the condition gradually grew worse until death on the fifty-fifth day. The other twin thrived. Various formulas were given, and for the last two weeks breast milk had been offered. There were frequent lavages with sodium bicarbonate, and atropine and other medicaments had been administered. Roentgenograms of the stomach one week before death revealed considerable retention of barium but no evidence of ulcer. At necropsy a large perforated gastric ulcer on the lesser curvature was found, involving one sixth of the gastric mucosa. The edges were rolled and the central area depressed. The perforation was at the proximal edge on the superoanterior aspect of the stomach near the liver. The gastric mucosa was pale and thickened, as was the pyloric ring. Plastic exudate was present on the liver and the spleen and in the pelvis. Microscopic examination showed an acute process with no attempt at repair. The cause is obscure, and the size of the infant precluded surgical intervention. Knowledge of the diagnosis beforehand would not have changed the type of treatment instituted.

AUTHORS' ABSTRACT.

A CASE OF HYPOCHLOREMIC VOMITING. A. F. A. S. WESTRIENEN, Maandschr. v. kindergeneesk. **10**:354 (June) 1941.

The author reports the case of a girl of 10 years who came into the hospital with the diagnosis of appendicitis; she suffered from abdominal pains and continuous vomiting for five days and nights. Determination of urea in the serum indicated the correct diagnosis: hypochloremic vomiting, a condition which soon disappeared after the usual therapy. The pneumonia was then revealed of which the original abdominal pain was the first symptom. With intervals of several months the condition repeated itself, but then no infectious disease was present. The clinical picture is discussed.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF CHOLASCOS IN A CHILD. J. L. KEYZER, Maandschr. v. kindergeneesk. **11**:56 (Nov.) 1941.

Keyzer reports a case of cholascos (accumulation of bile in the abdomen) caused by trauma, in a girl of 2 years. The high position of the diaphragm at the right side was peculiar. The heart was displaced to the left. Treatment consisted in repeated punctures, by which large amounts of bile were obtained. The girl recovered after four months.

VAN CREVELD, Amsterdam, Netherlands.

SEVERE ABNORMALITIES OF THE PANCREAS IN A CHILD. W. K. DICKE, Maandschr. v. kindergeneesk. **11**:155 (Feb.) 1942.

In the author's opinion the American figures on the frequency of cystic fibrosis of the pancreas in childhood probably also hold true for the Netherlands. The histories of 5 children who died and of 2 who are still alive are given.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF RUMINANT INFANTS. J. M. SOETERS, Maandschr. v. kindergeneesk. **11**:187 (March) 1942.

In the author's opinion in the treatment of rumination in babies, the movements of tongue and lower jaw should be prevented. He therefore immobilizes head and lower jaw with sandbags. The kind of feeding, provided that it is adapted to age and weight, is of no importance.

VAN CREVELD, Amsterdam, Netherlands.

HEMATEMESIS CAUSED BY AN ESOPHAGEAL POLYP IN A BABY. A. C. ROSMAN, Maandschr. v. kindergeneesk. **11**:217 (April) 1942.

A polyp which caused hematemesis in an infant was situated 1 cm. above the cardia.

VAN CREVELD, Amsterdam, Netherlands.

POURING OUT OF CHYLE INTO THE FREE ABDOMINAL CAVITY IN A BABY IN THE PRESENCE OF INTESTINAL INVAGINATION. B. M. TORDOIR, Maandschr. v. kindergeneesk. **11**:252 (May) 1942.

Chyle poured into the free abdominal cavity in a baby in the presence of intestinal invagination. The cause remained obscured.

VAN CREVELD, Amsterdam, Netherlands.

RELAPSING INFECTIOUS PAROTITIS (CHRONIC PAROTITIS WITH ACUTE EXACERBATION). T. HALBERTSMA. Maandschr. v. kindergeneesk. **12**:299 (Aug.-Sept.) 1943.

Two cases of relapsing infectious parotitis are reported. The patients were boys 8 and 2½ years old, respectively. In both cases streptococci could be cultured from the saliva. Both children had in the blood a high percentage of eosinophils (13 and 10 per cent, respectively), for which no explanation could be given.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF CONGENITAL AGENESIA OF THE EXTRAHEPATIC BILIARY DUCTS, WITH SOME REFERENCES TO VITAMINS A AND D. W. VAN ZEBEN, Maandschr. v. kindergeneesk. **12**:312 (Aug.-Sept.) 1943.

A case is reported of congenital agenesis of the extrahepatic biliary ducts. The child died at the age of 10 months. At the autopsy severe biliary cirrhosis was found. In the blood and in the liver no vitamin A could be demonstrated. Nevertheless, every indication of xerophthalmia was lacking. The existing rickets did not improve after administration of vitamin D orally. The phosphatase content of the blood was normal.

VAN CREVELD, Amsterdam, Netherlands.

Nervous Diseases

ST. LOUIS ENCEPHALITIS: OCCURRENCE IN CHILDREN IN THE ST. LOUIS AREA DURING NONEPIDEMIC YEARS 1939-1944. RUSSELL J. BLATTNER and FLORENCE M. HEYS, J. A. M. A. **129**:854 (Nov. 24) 1945.

During the years from 1939 to 1944 inclusive 66 cases of acute encephalitis were studied at the St. Louis Children's Hospital. Twelve were shown to be of the St. Louis type.

All 12 of these cases of St. Louis encephalitis occurred during the months May to October, and 9 of the 12 occurred during July, August and September. The occurrence of sporadic cases in the St. Louis area indicates the existence of an endemic focus. Recent advances in the epidemiology of this disease suggest a possible explanation for the persistence of such an endemic focus.

St. Louis encephalitis virus was not recovered from spinal fluid. However, during the course of these investigations the virus of lymphocytic choriomeningitis was recovered from spinal fluid in 1 instance and herpes simplex in another instance.

AUTHORS' SUMMARY.

PENICILLIN TREATMENT OF PNEUMOCOCCUS MENINGITIS IN INFANTS. GRETCHIN HUTCHINS and JOHN A. V. DAVIES, J. Pediat. **27**:505 (Dec.) 1945.

Pneumococcic meningitis has always been a serious disease, particularly in the younger age groups. Even with the use of specific antiserums and sulfon-

amide compounds the mortality rate was not reduced as much in infants as in older children and adults. This was thought to be due to the fact that infants under 2 years of age are more susceptible to pneumococcic infections and have a poorer immunologic response to this type of antigen.

Since penicillin was introduced for the treatment of pneumococcic meningitis new problems have arisen. These are illustrated by the analysis of 14 cases of this disease in which treatment was given in the Infants' and Children's Hospitals of Boston, between Sept. 30, 1943 and Dec. 28, 1944. It is shown that in 9 of these cases the patients lived, whereas there had been only three recoveries in this age group in the preceding fourteen years, when penicillin was not used. It is further pointed out that although the mortality rate is significantly reduced, the incidence of permanent damage of the central nervous system is high, especially in infants under 6 months of age and in those who had been ill for some time before treatment was started.

Penicillin was given in doses of 3,000 to 5,000 units intramuscularly every three hours, 10,000 units twice or three time a day and later on once a day intrathecally. In some cases sulfadiazine also was given. In a few cases injected spinal fluid was largely withdrawn and replaced with oxygen and the solution of penicillin. This was done to try to discourage the formation of fibrinous adhesions, which in some cases blocked the flow of cerebrospinal fluid and led to localized collections of pus or to secondary hydrocephalus.

Of the 14 patients treated during the period under discussion, 5 died; 1 who was 2½ months old when treated died two months after leaving the hospital, from residual cerebral damage. The 4 others had been sick from five days to two weeks before treatment was started. Four patients made good recoveries, the youngest being 3½ months old, and 5 others lived with residual damage of the central nervous system.

It was concluded that the younger the infant and the longer he or she had been ill before treatment was started, the poorer was the prognosis. Treatment should be started promptly with both sulfadiazine and penicillin—and the latter should be given both intrathecally and intramuscularly. Other forms of treatment to prevent adhesions and blocking of cerebrospinal fluid have not been evaluated.

AUTHORS' ABSTRACT.

CHOREA IN THE NEGRO RACE. W. A. DANIEL JR., J. Pediat. **27**:554 (Dec.) 1945.

A questionnaire was sent to each member of the American Academy of Pediatrics in the fourteen Southern states which form Region 2, requesting the pediatricians to report the number of cases of chorea occurring in the Negro children which they had seen. The total number of cases was requested without regard to the length of time the pediatrician had been in practice.

One hundred and twenty pediatricians reported a total of approximately 100 cases of chorea in Negro children. The general conclusions drawn from this survey were that chorea seems to be less common in the Negro than in the white child, less common in the "pure" Negro than in the mulatto but more severe in the former than in the mulatto. Whether the susceptibility to chorea is equal in the two races or whether the discrepancy is merely one of less accurate diagnosis in the Negro or is due to the fact that the majority of pediatricians reporting do not see large numbers of Negro patients cannot be determined. No accurate figures exist as to the total number of cases of chorea which occur in the two races.

Two questions arose as a result of the survey. If in the cases of chorea occurring in the "pure" Negro the disease is definitely severer than in the mulatto or white child, why is the disease so severe? Secondly, does the more stable nervous system of the Negro compared to the pampered white child play a factor in the development of chorea?

A fatal case of chorea was reported which occurred in an 11 year old "pure" Negro child.

AUTHOR'S ABSTRACT.

MENINGITIS CAUSED BY TYPE F HEMOPHILUS INFLUENZAE: REPORT OF A CASE WITH RECOVERY. JAMES G. PARKE, J. Pediat. **27**:567 (Dec.) 1945.

A 5 year old white boy was admitted to the hospital on Oct. 13, 1944, after vomiting and manifesting irritability, drowsiness and a temperature of 102 F. for two days. His neck and extremities were hyperextended, he was disoriented and he refused to take any food or liquids.

His respiratory rate was 25 to 35, the pulse rate was 125 and the skin was hot and dry. The ear drums were dark, the pharynx was injected and the nose was congested. The Kernig sign was positive bilaterally. The white cell count was 35,000, the cerebrospinal fluid was under high pressure and turbid and contained 9,500 cells per cubic millimeter.

A gram-negative bacillus was isolated from both spinal fluid and blood and was finally identified as Hemophilus influenzae, type f, in Dr. Pittman's laboratory in Washington, D. C.

Treatment was begun with 3.5 Gm. of sulfadiazine a day, and a whole blood transfusion of 200 cc. The temperature gradually dropped to 99 F., only to spike to 104 F. nine days after the patient's admission. Sulfathiazole and penicillin were then given, with a fall in temperature to 99 F. in nine days, once more. Administration of the sulfonamide drug was then stopped, and 70,000 units of penicillin were given intramuscularly per day and 10,000 units intrathecally every other day, for six more days. He became better oriented, but remained resistive and deaf. He was discharged afebrile, on the thirtieth hospital day.

Two months after his discharge he was greatly improved. The only residua were a slightly thin right leg, a weak right arm and questionable decreased hearing on the right.

Original and recent work on H. influenzae, especially in regard to meningitis caused by this agent, is discussed, and emphasis is placed on accurate typing of the organism in order to use the antiserum, if the causal agent is the usual type b, or to use other antibodies from the start, as was done in this case, since the antiserum is expensive, relatively dangerous and inefficient when used against types other than type b.

AUTHOR'S ABSTRACT.

THE USE OF PROSTIGMIN IN THE MANAGEMENT OF INFANTILE CEREBRAL PARALYSIS. PAUL N. JEPSON, J. Pediat. **28**:65 (Jan.) 1946.

Because of the lack of agreement as to the causation and preferred method of treatment in cases of infantile cerebral paralysis investigation was started in 1943 in an effort to improve the usually disappointing end results.

The traumatic factor seems to be the most frequent cause of the condition.

The essential principle involved in the treatment of the condition is one of training and rehabilitation over a prolonged period. Physical therapeutic measures are given with expectancy of greater improvement. Persistent reeducational measures are the sheet anchor of therapy.

In 1943 the oral administration of neostigmine bromide was begun in an attempt to reduce the muscular spasticity. It was found that a minimum dose of 5 mg. of neostigmine bromide given from five to eight times a day gave the maximum relaxation of musculature. The effect was satisfactory in children but not in adults. The younger the child the more relaxation was noted.

Results were noted as early as two to three weeks after the start of treatment. Administration of the drug should be continued for at least six months or until definite improvement is noted. After such a therapeutic program the patient apparently "learned" how to relax.

Twenty-five cases were cited. This paper is considered a preliminary report. It was written with the hope of stimulating further study and research.

AUTHOR'S ABSTRACT.

PREVENTION OF FORMATION OF END-BULB NEUROMATA. EDGAR J. POTH, E. BRAVO FERNANDEZ and GLENN A. DRAGER, Proc. Soc. Exper. Biol. & Med. **60**:200 (Nov.) 1945.

An extensive study with dogs revealed that end bulb neuromas could be prevented by encasing the proximal end of the severed nerve in a rigid tube or by injection of tannic acid solution or gentian violet medicinal. Because of the success attained in experimental animals in prevention of neuromas the authors believe it might be possible to prevent painful stump or fantom extremities in human beings undergoing amputation of a lower extremity. Multiple injections with 3 to 5 cc. of 2 per cent solution of gentian violet medicinal were made in 15 human beings undergoing amputation. The time elapsed is too short and the number of cases studied is too small as yet for conclusions to be drawn. However, the authors report that no patient suffered undue pain because of the procedure and that healing of the operative site was not compromised in any way.

HANSEN, Galveston, Texas.

CLASSIFICATION OF THE NERVOUS NEOPLASMS. M. SALAS MARTINEZ, Bol. méd. d. Hosp. inf., México **2**:205 (Sept.) 1945.

The author mentions the terminologies used by several of the best known authors, and after explaining the meaning and equivalence of the different terms he presents the following classification in order to facilitate a better understanding between the clinician and the pathologist.

I. Neoplasms of the nervous elements
1. Medulloblastoma
2. Retinoblastoma
3. Neuroblastoma
4. Ganglioneuroma

II. Neoplasms of the neurologic elements
5. Spongioblastoma multiforme
6. Spongioblastoma unipolare
7. Astroblastoma
8. Astrocytoma
9. Oligodendroblastoma
10. Oligodendrocytoma
11. Ependimoblastoma
12. Ependimocytoma
13. Pinealoblastoma
14. Pinealocytoma
15. Neurinoma

III. Neoplasms of the epitheliosecretory elements
16. Choriodoblastoma
17. Choriodocytoma
18. Chromaffinoma

The author believes that his classification offers the following advantages: 1. With few exceptions, its terms are the ones generally accepted. 2. The classification has a histogenetic basis which is the best accepted, at present, for classifying the neoplasms. 3. The names are formed in accordance with a general plan; each term is made up of the name of the original cell as the radical and the suffix "oma" as the ending. 4. The names, besides being simple, permit the easy recognition of the histologic nature and the manner of evolution of the neoplasms.

MADERO, México, D. F., Mexico.

INFLUENZAL MENINGITIS. J. VAN LOOKEREN CAMPAGNE, Maandschr. v. kindergeneesk. **11**:129 (Feb.) 1942.

Influenzal meningitis is a rather frequent and extremely serious disease in young children, practically always caused by subtype b (Cohen-Pittman) of Haemophilus influenzae. Treatment with specific antiserum has brought a slight improvement in the prognosis. Much more efficacious are sulfanilamide and other sulfonamide compounds, the best of which for the present seems to be sulfapyridin, which also has proved to be active against Haemophilus organisms in vitro and after animal inoculation. The prognosis of influenzal meningitis now seems to be rather favorable if enough sulfapyridine is given (150 to 250 mg. per kilogram daily), when the child is older than 2 years and comes under treatment in the very beginning of the illness.

VAN CREVELD, Amsterdam, Netherlands.

ACUTE PURULENT MENINGITIS, CAUSED BY BACILLUS FAECALIS ALCALIGENES. M. E. S. HENNEMANN, Maandschr. v. kindergeneesk. **11**:246 (May) 1942.

The author reports on a case of acute purulent meningitis caused by Alcaligenes faecalis in a boy 1 year old.

VAN CREVELD, Amsterdam, Netherlands.

PUBERTAS PRAECOX IN A GIRL OF TWO YEARS WITH A TUMOR OF THE LEFT CORPUS MAMILLARE. C. HOOFT, K. DIERICKX and P. CIETERS, Maandschr. v. kindergeneesk. **12**:87 (Jan.) 1943.

The clinical and pathologic history is given of a girl aged 2 years with pubertas precox of central origin. The pathologic investigation revealed the existence of a circumscribed tumor (hyperplasia?) of the left corpus mamillare. The importance of this case lies in the fact that a tumor (hyperplasia?) of one corpus mamillare, without symptoms of pressure on the neighboring hypophysis and with absence of dilatation of the ventricles, could give rise to precocious puberty. The symptoms became evident about the sixth or seventh month after birth, so that it can be said almost with certainty that the tumor was congenital. Further particulars are the herculean type of the child, the hypercholesterinemia and the hyperglycemia.

VAN CREVELD, Amsterdam, Netherlands.

OCCASIONAL CONVULSIONS. C. DE LANGE, Maandschr. v. kindergeneesk. **12**:179 (April) 1943.

In 2 cases of so-called transitory convulsions with high temperature the brain was examined. Both children were in the onset of bronchopneumonia and were respectively 17 and nearly 12 months old. Meningitis serosa was absent; the only anomaly proved to be a homogenization of the Purkinje cells. In the second child the number of uninuclear elements in the pia arachnoidea was, moreover, slightly increased. Perhaps the illness had been too short to produce histologic alterations of cells and tissues. The author has never found tetanus to be the cause of transitory convulsions.

VAN CREVELD, Amsterdam, Netherlands.

FACIAL PARALYSIS AND APLASIA OF BRAIN NUCLEI. A. G. SCHOO, Maandschr. v. kindergeneesk. **12**:232 (May) 1943.

Three cases of agenesis are reported and the theory of its origin of Moebius, Heubner and C. de Bonnevie is given.

VAN CREVELD, Amsterdam, Netherlands.

CEREBRAL TUMORS IN CHILDREN. A. C. DE VET, Maandschr. v. kindergeneesk. **12**:243 (June) 1943.

The author gives a review of the cerebral tumors in childhood. His principal conclusions are as follows: 1. The clinical symptoms differ in several respects from those in the adult. 2. Certain types of cerebral tumors are found more, others less, often among children, while still others are lacking altogether. 3. Among children the tumor is more frequently found in the posterior fossa than above the tentorium. 4. One encounters malignant tumors relatively more often. 5. The results of neurosurgical intervention are thus less often successful than among adults. As, however, the prognosis must otherwise be rather unfavorable, it is necessary in those cases in which the possibility of success exists, even though it may seem to be small, to risk an attempt at operative extirpation. The value of symptomatic therapy (decompression) must not be underestimated.

VAN CREVELD, Amsterdam, Netherlands.

SYNDROME OF GUILLAIN-BARRÉ IN A CHILD OF TWO YEARS. Y. M. TRAP, Maandschr. v. kindergeneesk. **13**:147 (May) 1944.

The syndrome of Guillain-Barré in a boy 2 years and 4 months old is described. The limbs and the trunk were paralyzed, but the muscles of the arms recovered

in the course of some months. One and one-half years after the inception of the disease the legs still were partly paralyzed.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Genitourinary Tract

LIPEMIC NEPHROSIS. WALTER HEYMANN and VIOLA STARTZMAN, J. Pediat. **28**: 117 (Feb.) 1946.

Thirty-four children suffering from primary lipemic nephrosis have been observed within the last twelve years. At the onset, 64 per cent were under 3 years of age. Twenty-one per cent were from 4 to 7 years and 15 per cent were from 9 to 11 years of age when the disease began. These figures demonstrate its decreasing incidence among older children and explain its rare occurrence in adults. Lipemic nephrosis is rare in the Negro race.

Six postmortem examinations are discussed. The microscopic examination in 3 cases showed no signs of inflammatory disease, and azocarmine stains revealed normal, not thickened glomerular basement membrane. In the 3 remaining cases, renal inflammatory disease was found in addition to definite nephrotic changes. In only 1 of these were there slightly thickened basement membranes. On the basis of these and the clinical observations it is concluded that there are (1) primary lipemic nephosis, (2) primary nephritis which results secondarily in the nephrotic syndrome and (3) primary lipemic nephrosis which results secondarily in nephritis. The inflammatory lesion in the latter instance is usually of the interstitial and pyelonephritic type.

The chronicity of the disease should not be included in the terminology. Three children are reported on who were ill for only two, four and twelve weeks. Two of these recovered spontaneously, whereas the third recovery followed an overdose of thyroid extract. In spite of severe intercurrent infections frequently observed, the authors cannot state that these either improved or cured the nephrotic disease. Thus, it is not recommended that chemotherapy for intercurrent infections be delayed. Mumps and pertussis occurred in 4 of the nephrotic children. A temporary aggravation was seen during the acute phase of these infections. One out of 4 children who acquired measles died from pneumonia, whereas the urine of 2 others became albumin free for four to eighteen days. Temporarily the edema and the ascites disappeared, and there was a transient improvement in the chemical composition of the blood. The condition of the fourth patient who had measles temporarily became worse. Even though it is admitted that measles may temporarily improve the condition of a patient with lipemic nephrosis, the "rumor" that it cures nephrosis cannot be substantiated.

It has been shown that hypoproteinemia and hypoalbuminemia do not entirely explain the formation of edema in nephrosis. There are several other factors involved in this mechanism. The endogenous origin of the hyperlipemia of nephrosis is shown by the fact that it is not affected by diets of either low or high fat ratios, and that the nephrotic hyperlipemia does not decrease when 30 to 40 Gm. of soya bean lecithin is given for four weeks. Clinical data do not support the hypothesis that the hyperlipemia is due to the hypoproteinemia, nor do they agree with the conception that the nephrotic renal damage is due to a primary disturbance of fat metabolism. It has been shown in experiments with animals that the kidneys are involved in a mechanism which regulates concentration of lipids in the blood. On the basis of these studies the hypothesis is advanced that the hyperlipemia in nephrosis is of renal origin.

As for therapy, the authors recommend a salt-free diet containing 3 Gm. of protein per kilogram of body weight and a fluid intake limited to 1,200 to 1,500 cc. in combination with thyroid extract. This is increased every ten days by ½ grain (33 mg.). As soon as toxic symptoms are observed, the dose is reduced by ¼ to ½ grain (16 to 33 mg.) and kept as a maintenance dose for two to three months. If after two weeks of bed rest thyroid medication and dietary treatment, the

edema and the ascites have not appreciably decreased, daily intravenous infusions of from 200 to 300 cc. of plasma are given and continued for three to six weeks if necessary. Under the prophylactic administration of 0.1 Gm. per kilogram of body weight of sulfadiazine or sulfathiazole, abdominal paracentesis may be performed without risk, if the abdominal distention is excessive. Intercurrent infections are treated with 0.1 to 0.2 Gm. of a sulfonamide drug per kilogram of body weight or with penicillin if indicated.

Twelve children were reexamined up to seventeen years after their first discharge from the hospital. Only 1 of these had a severe chronic nephritis. Eight were certainly and 3 probably cured. Three out of the 8 completely reexamined patients had an orthostatic albuminuria five, six and eight years, respectively, after the onset of the nephrosis. The ultimate prognosis of primary lipemic nephrosis is better than is generally believed. The mortality rate of 30 per cent which the authors have had in their series of 34 patients is not valid today. Most of these patients were treated before the described therapeutic regimen was instituted. According to the authors' observations in 11 cases in which treatment was given during the last three years the present mortality rate would be between 15 and 20 per cent.

AUTHORS' ABSTRACT.

Diseases of the Ductless Glands; Endocrinology

INFLUENZA AND BILATERAL ADRENAL HEMORRHAGE. M. STRAUB and A. v. WESTRIENEN, Maandschr. v. kindergeneesk. **11**:177 (March) 1942.

A baby of 3 months, breast fed, who had been ill for a month, was taken into the hospital with symptoms of bronchopneumonia; the child was extremely emaciated and exsiccated. Physical examination of the thorax and the roentgenologic examination showed an atelectasis of the right lung with dislocation of the heart to the right. However, in the dense shadow at the right side on the roentgenogram here and there some clear spots were visible, as well as an extremely wide main bronchus with ramifications. The possibility of a congenital malformation was considered. The baby died on the second day after its entrance into the hospital. At autopsy a hemorrhagic infarction of both adrenal glands was found. At the histologic examination of the epithelium of trachea and bronchi abnormalities were found which resembled those obtained by Straub by inoculation of mice with influenza virus of man and pig.

The combination of emphysematous and atelectatic parts in the lungs caused by obstruction of the small bronchi is characteristic of this this disease and may be recognized during life on the roentgenogram.

VAN CREVELD, Amsterdam, Netherlands.

RESPONSE OF A PATIENT WITH DIABETES TO THREE EQUAL MEALS. F. GERRITZEN, Nederl. tijdschr. v. geneesk. **87**:976 (May 22) 1943.

A method is described to determine the response of the diabetic patient to three equal meals daily. On the basis of this response, diabetic persons can be divided into three groups: Patients with mild disease who do not need insulin, patients who should receive two injections of insulin and patients with severe disease for whom, besides common insulin, preparations with prolonged action may be useful.

The value of this test is considered, with special regard to the problems raised by the present scarcity of insulin.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Muscles, Bones, Joints and Lymph Glands

MULTIPLE MYELOMA IN A FIFTEEN-YEAR OLD BOY. MICHAEL A. RUBINSTEIN, New York State J. Med. **44**:2491 (Nov. 15) 1944.

A case of multiple myeloma of the plasma cell type in a 15 year old boy is reported. Symptoms began at the age of 12 years. Lesions were found in a

humerus, a femur, the ribs and the skull. Diagnosis was made by sternal marrow biopsy, by biopsy of one of the skull lesions and by the finding of Bence Jones protein in the urine and high levels of albumin and euglobulin in the serum.

The unusual occurrence of the disease at this age is discussed.

DAVIS, Rochester, N. Y.

OPPENHEIM'S DISEASE. G. CASTILLO DÍAZ and F. BLANCO, Bol. méd. d. Hosp. inf., México **1**:68 (March) 1944.

Consuelo G. G., a 21 month old girl, was seen in the outpatient department on Sept. 2, 1943. The patient had never been able to move or sit. She remained always in the same posture in which she was left. The muscles were completely relaxed, but not atrophied. The reflexes were absent. There was a slow response to electric excitation. These and other observations and laboratory tests led to the diagnosis of myatonia congenita.

The patient improved slowly under the proper treatment but died a month later of an intercurrent disease.

MADERO, México, D. F., Mexico.

FAMILIAR OSTEOGENESIS IMPERFECTA (TYPE VROLIK) AND ITS TREATMENT WITH VITAMIN D SHOCK. EDWARD GLANZMANN, Bull. d. schweiz. Akad. d. med. Wissensch. **1**:180, 1945.

The author describes 2 rare cases of osteogenesis imperfecta of Vrolik's type, in a brother and sister, with rhizomelic micromelia and acrocephaly accompanied by exophthalmos, which, however, did not present a clear blue coloring of the sclera. Whereas the boy lived for only five months (life is usually short in such cases), the girl reached the age of 9 years. The author tried, for the first time with success, repeated shock treatments with vitamin D which provoked normal osteogenesis, confirmed by roentgenologic examination, and prevented new fractures from occurring.

AUTHOR'S ABSTRACT.

Diseases of the Eye

PROGNOSIS OF CONGENITAL CATARACT AND OF CATARACT OCCURRING DURING THE FIRST YEARS OF LIFE. C. D. BINKHORST, Nederl. tijdschr. v. geneesk. **87**:343 (Feb. 20) 1943.

The operative results of 97 cases of cataracts of infants and adolescents are reported. While the operative results of unilateral cataracts were bad, those of the bilateral cataracts proved to be satisfactory. The operation on total cataracts and on cataracts with nystagmus appeared to have in general a worse result than the operations on partial cataracts and on cataracts without nystagmus.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF OGUCHI'S DISEASE TYPE I IN THE NETHERLANDS. J. TEN DOESSCHATE, Nederl. tijdschr. v. geneesk. **87**:636 (April 3) 1943.

A review of the literature on Oguchi's disease is given, followed by a description of a case in a girl 17 years old, observed by the author in the Netherlands. A new argument is supplied in favor of the theory that there is no direct causal connection between the "phenomenon of Mizuo" and the disturbance in adaptation which is one of the symptoms of Oguchi's disease.

VAN CREVELD, Amsterdam, Netherlands.

Skin Diseases; Allergy

LEINER'S DISEASE FOLLOWED BY THE CELIAC SYNDROME: A CASE REPORT. H. E. THELANDER, J. Pediat. **28**:101 (Jan.) 1946.

A. B., a girl born of normal, healthy parents, contracted at the age of approximately 6 weeks a desquamating disease, nonallergic in origin, which did not respond to any known treatment and which ran a course like that of Leiner's disease to the age of about 5 months, when spontaneous recovery occurred. After this illness the child remained well and developed normally up to the age of 8 months. At the age of 8 months, when on a rather strenuous vacation trip, the child had diarrhea. She was not seen by the author for a period of one month. During that time she had lost 3½ pounds (1,534 Gm.) and presented the picture of celiac syndrome. She was followed from the age of 9 months until 5 years and ran the course of a patient with typical celiac disease. The final report at the age of 8 years found her completely recovered and developing normally physically and mentally.

The case is reported because of the occurrence in the same patient in rapid sequence of two poorly understood syndromes. Although it is possible that this was mere coincidence, it seems worth while to point out the following: (1) that among the many therapeutic measures suggested by various authors for Leiner's disease is that of a diet low in carbohydrates and fats; (2) that Glaser reported observing pathologic conditions in the liver and the pancreas in his patient, and (3) that present knowledge of the relationship between deficiencies, causal or resultant disease, and intestinal and cutaneous condition is meager. The occurrence of the two syndromes in the same patient may point to a common causal factor.

AUTHOR'S ABSTRACT.

CONGENITAL ECTODERMAL DEFECT. J. LAMAR CALLAWAY, RAY O. NOOJIN, KATHLEEN A. RILEY and BEATRICE H. KUHN, J. Pediat. **28**:214 (Feb.) 1946.

The first report of congenital ectodermal defects of the scalp was made by Anderson and Novy in 1942.

Among the causes which have been suggested are amniotic adhesions, hereditary factors, arrested development, intrauterine healing of angioma and pressure necrosis of the extremities and of the scalp during labor. Clinical characteristics are relatively consistent. The majority of the lesions are single, and they are usually located in or near the midline and most commonly on the vertex. The size of the lesion averages 1 to 2 cm., and the largest reported lesion measured 60 sq. cm. The lesions are usually oval in configuration and only occasionally elongated or irregular. In a majority of cases only the epidermis and the subcutaneous tissues were involved. The lesion may extend to the dura, the pericranium or the glia. The gross features show considerable variations, but the lesions are usually described as consisting of scarlike tissue and as having sharp punched-out margins. At first a dry translucent membrane covers the area; this later breaks down, leaving granulation tissue. Despite occasional variations in gross appearance, the absence of hair tends to be a consistent feature. Eight per cent of the cases reported have been associated with a congenital defect elsewhere.

The diagnosis is based on the presence of the aforementioned criteria at birth. In the differential diagnosis criminal injury, forceps injury, primary syphilis and congenital depression of the skull are to be considered.

The prognosis is less favorable for defects of the scalp than for ectodermal defects elsewhere because of the danger of increased injury to the lesion during delivery.

There seems to be no treatment indicated except the prevention of trauma and secondary infection by the use of local bland therapy. A case is reported of a girl, 3 weeks old, with lesions of the scalp and of the left leg. The child was normal in every way except for the cutaneous lesions. There was a lesion on the

right vertex which was 8 by 6 cm. in size and was covered with a transparent membrane. Scar tissue was present along the borders of the affected area. The left leg had a similar lesion that formed an encircling band about the ankle 3 cm. in width. Both lesions showed atrophy, especially the lesions on the ankle, where there was some deformity due to fibrosis and scarring. The lesions were treated with a simple boric acid ointment plus massage to the left ankle. One month after the child was first seen the lesions showed signs of regression, with the formation of more scar tissue and only slight deformity of the left ankle.

AUTHORS' ABSTRACT.

Surgery and Orthopedics

WOUND INFECTIONS CAUSED BY A CARRIER OF BACILLI. J. C. VERHAGE, Maandschr. v. kindergeneesk. **13**:113 (March) 1944.

In a surgical department many cases of serious infection of wounds occurred, especially after simple operations. All patients had been operated on by the same physician, whose throat contained numerous hemolytic streptococci.

In another surgical department of a children's hospital a number of infections occurred, caused by diphtheria bacilli; here probably a carrier of bacilli had caused the spreading of the infection. The significance of carriers of bacilli for the occurrence of infection of wounds in hospitals is stressed.

VAN CREVELD, Amsterdam, Netherlands.

Teeth and Dentistry

EPIDEMIC OF STREPTOCOCCIC INFECTIONS CAUSED BY A GERM CARRIER IN A SURGICAL DEPARTMENT. J. C. VERHAGE and W. HEKMAN, Nederl. tijdschr. v. geneesk. **87**:536 (March 20) 1943.

An account is given of an epidemic of infections in a surgical department, caused by hemolytic streptococci which came from the throat of a carrier. These hemolytic streptococci had various effects, such as purulent infections of wounds with an exanthema which was not characteristic of scarlet fever, erysipelas, wound scarlet fever and ordinary scarlet fever.

VAN CREVELD, Amsterdam, Netherlands.

Miscellaneous

ORAL PLASMA FEEDING. JOHN F. LOEHLE, J. Pediat. **28**:145 (Feb.) 1946.

Loehle is convinced that his results with oral feeding of plasma justify the incorporation of protein, in some form or other, in neonatal feedings. He stressed this particularly with regard to premature infants and full term infants who failed to gain weight.

Wilhelm von Mollendorf observed that trypan blue, which normally passes body membranes slowly (probably through phagocytes), and casein, which normally must be digested before it can be absorbed, penetrate the intestinal epithelium rather rapidly in neonatal life. This situation is altered as the digestive juices appear, to approach the ordinary form of epithelial penetration.

This foreknowledge led Loehle to conclude that too little emphasis had hitherto been placed on colostrum studies and colostrum feeding, because woman, differing from all other mammals, produces colostrum first and foremost, while nature holds in abeyance, as it were, the lactogenic forces of parturition, which in all other mammals, are concomitant with or precede parturition.

Colostrum, although containing fat globules, of which little is known, resembles plasma in general characteristics more closely than human milk; like plasma it is a transudate, whereas milk is a glandular secretion.

Acting on this observation, Loehle fed 7 premature infants, ranging in body weight from a low of about 1,720 Gm. to a high of about 2,500 Gm., plasma by mouth, accompanied by nothing else, for twenty-four hours; the plasma was added thereafter to the variously constituted neonatal feedings. In all cases, loss of neonatal weight ceased and the infants thrived and gained. When the plasma was subtracted from the feedings the infants promptly lost weight.

To obviate the possibility of coincidence in the interpretation of results, Loehle fed three sets of twins, all of comparable weights, plasma orally, alternating the feedings so as to have at all times a plasma-fed infant and, as a control, an infant not fed on plasma. The accompanying charts reveal beyond doubt the advantages of oral administration of plasma.

Several abnormal full term infants were fed plasma. The most striking result was noted in a 2 month infant, who had, it was subsequently discovered at operation, pyloric stenosis bordering on atresia. Similarly, a first-born boy, whose loss of weight was attended with protracted vomiting, had plasma added to the prescribed feeding. The vomiting stopped, and there followed an improvement in weight gain and general condition little short of phenomenal.

This elimination of vomiting and the absence of gastrointestinal irritation prompted Loehle to believe that plasma may act as a natural antacid or may in some peculiar manner alter the curding process of cow's milk. There is also the possibility that estrogenic, vitamin and immune substances could prove an added benefit to the newborn, and especially to the premature in this type of feeding.

The method adopted for oral feeding of plasma was to administer 10 cc. of plasma per kilogram with an equal amount of solution of honey every two hours for the first twenty-four hours. If the body weight of the infant remains the same, or increases after the first twenty-four hours, the feedings are spaced two and one-half hours apart for the second twenty-four hours. If progress is noted on the third day, the feedings are spaced three hours apart, and thereafter the plasma is added to the feedings of choice.

In Loehle's opinion this type of feeding is little else but an intestinal transfusion of essential proteins, not necessarily associated with the complexity of plasma protein digestion.

AUTHOR'S ABSTRACT.

ONE DOSE SUBCUTANEOUS SODIUM SULFADIAZINE FOR ACUTE INFECTIONS. KURT GLASER, J. Pediat. **28**:187 (Feb.) 1946.

The oral administration of sulfonamide compounds in a single dose has been suggested by several authors. It was thought that there would be less risk of toxic manifestations or sensitization to the drug and that there would be a reduction in cost. The author thought of further improving this method by administering a 5 per cent solution of sodium sulfadiazine in distilled water subcutaneously, thus avoiding the enteral route. The dosage was approximately 1 grain per pound (143 mg. per kilogram) of body weight. The drug was injected in a single procedure in one or both thighs. Twenty-four patients with infections of the upper or the lower respiratory tract were treated. Ten of them had pneumonia, as was proved roentgenologically. Of these 24 patients, 19 received the one injection as their only sulfonamide treatment and recovered rapidly without any untoward local symptoms. Some patients showed crystalluria and hematuria, which cleared up within a few days. In 5 of the 24 cases, sulfonamide treatment was continued after the initial dose, because complications such as empyema and mastoiditis developed. The dosage, weight, temperature, blood count, urinalyses and levels of sulfadiazine in the blood were tabulated in detail in all cases. In his summary the author recommends this type of treatment for patients in their homes, especially in rural communities where hospital facilities and trained personnel are wanting. He discourages the use of this method in pneumonia with complications or for seriously ill patients.

AUTHOR'S ABSTRACT.

INVESTIGATION INTO THE CAUSE OF CYANOSIS AFTER THE USE OF SULFANILAMIDE, SULFAPYRIDINE AND SULFATHIAZOLE PREPARATIONS. J. K. KRAAN and L. VAN VEEN, Nederl. tijdschr. v. geneesk. **86**:825 (April 4) 1942.

In 34 out of 37 patients to whom preparations of sulfanilamide, sulfapyridine or sulfathiazole had been given, methemoglobin could be demonstrated in the blood. In 5 of them, and in the remaining 3 patients, a further substance was formed, which proved to be reversible and was able to produce severe toxic symptoms. The greatest changes were produced by sulfanilamide. Sulfapyridine gives somewhat less intense alterations, and the preparations of sulfathiazole the least severe ones.

VAN CREVELD, Amsterdam, Netherlands.

COMMENTS ON THE USE OF SULFAPYRIDINE. C. L. C. VAN NIEUWENHUIZEN and J. A. VAN LOON, Nederl. tijdschr. v. geneesk. **86**:890 (April 11) 1942.

Injection of 50 to 100 mg. of nicotinamide about fifteen minutes before the administration of sulfapyridine has a favorable effect on the vomiting caused by this drug.

Preexisting leukopenia need not contraindicate a forced course of sulfapyridine. Leukopenia arising during a course of sulfapyridine can be effectively checked by an intramuscular dose of 10 cc. of sterilized milk. It is proposed that these two therapeutic measures be applied in combination in endocarditis lenta.

VAN CREVELD, Amsterdam, Netherlands.

INFLUENCE OF HYPEROXIA ON THE CUTANEOUS CONSUMPTION OF OXYGEN. R. BRINKMAN, Nederl. tijdschr. v. geneesk. **86**:1350 (May 30) 1942.

By tracing the oxygen saturation of the capillary blood of the heated skin of the finger after sudden ligaturing of its circulation it is shown that the rate of oxygen consumption in the tissue is noticeably diminished when the intracapillary oxygen tension is raised by oxygen ventilation.

VAN CREVELD, Amsterdam, Netherlands.

ROENTGENOLOGICALLY DIAGNOSED PREGNANCY OF QUADRUPLETS. A. P. W. WEBER, Nederl. tijdschr. v. geneesk. **87**:1173 (June 26-July 3) 1943.

Quadruple pregnancy was roentgenologically diagnosed. After a pregnancy of two hundred and twenty-two days (nearly thirty-two weeks) a boy and three girls were born, all in breech presentation. The children all were in good condition. Examination of the placenta showed that the boy had a chorion as well as an amnion of his own; the three girls had the chorion in common, while each of them had an individual amnion. From this it can be concluded that the quadruplets originated from two ova, one for the boy and another from which the three girls developed.

VAN CREVELD, Amsterdam, Netherlands.

News and Comment

GENERAL NEWS

Eleventh Congress of the Association of French-Speaking Pediatricians.—The Eleventh Congress of the Association of French-Speaking Pediatricians will be held in Lyon, France, on May 22, 23 and 24, 1947, under the presidency of Prof. G. Mouriquand.

The subjects to be discussed will be as follows:

Chronic Rheumatism During Childhood, by M. Lamy.

Malignant Neoplasms of the Thoracic and Abdominal Cavities During Childhood (Tumors of Nervous Tissue Excepted), by L. Caussade and M. Guilleminet.

Treatment of Acute Meningitis During Childhood (Tuberculous Meningitis Excepted), by R. Martin.

The Congress will be followed by an excursion to Mégève, Saint-Gervais and Chamonix on Sunday and Monday (May 25 and 26).

Further information regarding the Congress may be secured from the Secretary General, Dr. M. Jeune, 24, Place Bellecour, Lyon, France.

First Pan-American Congress of Pediatrics.—The First Pan-American Congress of Pediatrics will be held at the Mayflower Hotel, Washington, D. C., July 9 to 12, 1947, under the auspices of the American Academy of Pediatrics. Dr. Felix Hurtado, of Habana, will be the presiding officer.

NOTICE

Application Fee for the American Board of Pediatrics, Inc.—Because of the increased cost of running the American Board of Pediatrics, Inc., the Board has found it necessary to raise the application fee to $125, effective May 1, 1947.

Book Reviews

The Clinical Application of the Rorschach Test. Second edition. By Ruth Bochner, M.A., and Florence Halpern, M.A. Price, $4. Pp. 331. New York: Grune & Stratton, Inc., 1945.

This is a well written, understandable book which describes the purpose, method of administration and ways of scoring the Rorschach test. This test consists in showing the patient ten standardized ink spots and asking him to give his interpretation of them. The results are free associations of the patient from a stimulus without content. They are therefore a projection of the personality of the patient. The scoring is essentially symbols of the responses. From studies of a large number of patients (or other persons) it is possible to recognize personality responses, for instance neurotic and schizophrenic. The book describes in detail the responses and the method of scoring the records of 32 patients.

Das Herz beim Scharlach. By Bernhard Steinmann, M.D. Price, 12.80 Swiss francs. Pp. 149, with 21 illustrations. Berne, Switzerland: Hans Huber, 1945.

Steinmann has studied 350 cases of scarlet fever clinically, roentgenologically and electrocardiographically. He has come to the conclusion expressed by students of scarlet fever everywhere, that myocarditis can often be demonstrated in this disease. Myocardial disturbance has been specifically pointed out by Toomey as being a concomitant feature of the disease. The author makes the distinction between early minor and late cardiac involvements—late as seen in the second to fourth week of the disease, often in older children. This distinction is not clearcut, probably being merely relative. Steinmann produced myocardial disturbances experimentally in rabbits by injecting Dick toxin. He feels that there is a difference between scarlatinal and rheumatic carditis, a difference which is not admitted by all students of the disease. Many of the American workers believe that all these conditions are late results of streptococcicoses in the sense described by Powers of Yale.

Synopsis of Physiology. By Rolland J. Main, Ph.D., Late Professor of Physiology, Medical College of Virginia. Price, $3.50. Pp. 341, with illustrations. St. Louis: C. V. Mosby Company, 1946.

Even a cursory examination of the book will readily convince the reader that the author has spent a great deal of time in condensing the physiologic facts and their clinical applications into this pocket-sized volume. It is a splendid book for the student or the clinician who wishes to review physiology, for one purpose or the other. Most of the recent advances have been briefly incorporated. The reviewer failed only to note the inclusion of "pancreozymin," the hormone responsible for increasing the enzyme content of pancreatic juice, since pancreatic secretin is responsible only for an increase in the volume and total saline content of pancreatic juice. It should be noted, however, that perusal of the book demands a fairly adequate physiologic fund of information, since the author simply refers to material with which the reader presumably was at one time conversant.

The American Hospital. By E. H. Lewinski-Corwin, Ph.D. Price, $1. Pp. 226. New York: The Commonwealth Fund, 1946.

From the genesis of hospitals in the United States, which began with Benjamin Franklin as one of the moving spirits in the establishment of the Pennsylvania Hospital in Philadelphia in 1751, one finds in this book a study of the broad development of hospitals which proceeded from this beginning to the present day, when there are 6,655 hospitals. As late as 1873 there were only 178 hospitals listed for bed care in this country. Between 1873 and 1946 an unusual story is

told in facts, figures and charts, which shows the growth and development of hospitals.

The expansion of hospital facilities in the last fifty years has exceeded several-fold the increase in population and is the result of the phenomenal development of medicine and surgery, the growth in wealth and the urbanization of the country. Although many types of hospitals have been created, the general hospital occupies the center of interest. While it accounts for only 40 per cent of the bed capacity, it admits 90 per cent of all the patients who enter the hospitals within a year. One realizes the influence and the obligation which hospitals have when one considers that each year 1 out of 10 persons is hospitalized—not to mention those who receive care in clinics and as ambulatory patients.

As one reads this history of hospitals, so ably and interestingly presented by the author, one realizes the contribution which has been collectively made by independent organizations operated not for profit in the interests of the public. In addition to the care of the sick, the education and training of physicians, nurses, technicians and other personnel to man these complicated organizations have been necessary to the growth of hospitals, so that today some 550,000 full time employees are needed.

History in itself is interesting, but having come this far the author summarizes in the last chapter the past in "restrospect" and looks to the future with "prospect." What lies ahead is more absorbing, in terms of the possibility of meeting some of the needs which are indicated. First, convalescent care is an indispensable complement to hospital treatment. Second, it is suggested that 238,300 more beds are needed for additional hospital facilities for the care of the general, the mental and the tuberculous patient, and 178,800 beds for replacement of present obsolete facilities, at an estimated total investment of $2,065,300,000. The new beds are mainly suggested to even out the distribution of hospital facilities, despite the fact that 98.5 per cent of the population live within 30 miles (48 kilometers) of a recognized hospital. Third, the extension of insurance plans to help the public budget the cost of hospital care. These and other problems are presented for solution in the days which lie ahead.

This book represents a real contribution to the hospital field because it is highly informative and brings together from many sources much valuable material, and it should indicate to those who are in the field, and those who are not, the complexity of running a modern hospital.

Mitchell-Nelson Textbook of Pediatrics. Edited by Waldo E. Nelson, M.D., with the Collaboration of Forty-Nine Contributors. Fourth edition. Price, $10.00. Pp. 1350, with 335 figures and 97 tables. Philadelphia: W. B. Saunders Company, 1945.

The Mitchell and Nelson "Pediatrics" is a fourth revision of Griffith and Mitchell's original textbook. However, the new volume bears little resemblance to its predecessors. Under the editorship of Dr. Waldo E. Nelson, forty-nine authors have contributed to the various sections. Emphasis is placed on an understanding of the physiologic and biochemical foundation for rational diagnosis and treatment of the infant and child. Growth and development and the stresses imposed thereby are completely, though concisely, treated. The sections devoted to these phases of the subject leave little to be desired for teaching or for reference purposes. Throughout, one is impressed by the careful organization and the logical arrangement of the context. Considering the necessarily broad scope of such a volume, the relative completeness of the bibliography accompanying each section and the frequent references in the text to source material are gratifying.

A short section at the end of the book devoted to such technical data as normal laboratory values, body measurements, fluid requirements, drug dosage and conversion tables and the caloric values of most standard food will be welcomed by medical student and practicing physician alike.

In summary, this is an excellent and complete textbook of pediatrics, which should prove to be equally valuable as a text for use in teaching or as a reference.